WEST Search History

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DATE: Friday, December 29, 2006

Hide?	Set Name	Query	Hit Count
		DB=USPT; PLUR=YES; OP=AND	
☐	L31	kanesa-thasan-niranjan.in.	1
☐	L30	sun-wellington.in.	0
☐	L29	L28 not L20	0
☐	L28	hoke-charles-h.in.	5
☐	L27	L26 not L20	0
☐	L26	innis-bruce-l.in.	5
☐	L25	innis.in.	104
☐	L24	L23 not L20	1
☐	L23	L22 and dengue	6
☐	L22	dubois-doria-r.in.	6
☐	L21	dubois.in.	925
☐	L20	L19 and dengue	8
☐	L19	putnak.in.	8
☐	L18	putnak-joseph.in.	0
☐	L17	eckels-kenneth.in.	2
		DB=PGPB; PLUR=YES; OP=AND	
☐	L16	kanesa-thasan.in.	0
☐	L15	thasan.in.	0
☐	L14	kanesa.in.	0
☐	L13	sun-wellington.in.	0
☐	L12	L11 and dengue	0
☐	L11	hoke.in.	85
☐	L10	L9 and dengue	1
☐	L9	innis.in.	29
☐	L8	L7 not L5	2
☐	L7	L6 and dengue	2
☐	L6	dubois.in.	260
☐	L5	L4 and dengue	1
☐	L4	putnak.in.	1
☐	L3	s L1 and dengue	0
☐	L2	eckels-kenneth.in.	0

☐	L1	eckels.in.	82

END OF SEARCH HISTORY

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* * * * * * * * * *  Welcome to STN International  * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  AUG 09  INSPEC enhanced with 1898-1968 archive
 NEWS  4  AUG 28  ADISCTI Reloaded and Enhanced
 NEWS  5  AUG 30  CA(SM)/CAplus(SM) Austrian patent law changes
 NEWS  6  SEP 21  CA/CAplus fields enhanced with simultaneous left and right
                  truncation
 NEWS  7  SEP 25  CA(SM)/CAplus(SM) display of CA Lexicon enhanced
 NEWS  8  SEP 25  CAS REGISTRY(SM) no longer includes Concord 3D coordinates
 NEWS  9  SEP 25  CAS REGISTRY(SM) updated with amino acid codes for pyrrolysine
 NEWS 10  SEP 28  CEABA-VTB classification code fields reloaded with new
                  classification scheme
 NEWS 11  OCT 19  LOGOFF HOLD duration extended to 120 minutes
 NEWS 12  OCT 19  E-mail format enhanced
 NEWS 13  OCT 23  Option to turn off MARPAT highlighting enhancements available
 NEWS 14  OCT 23  CAS Registry Number crossover limit increased to 300,000 in
                  multiple databases
 NEWS 15  OCT 23  The Derwent World Patents Index suite of databases on STN
                  has been enhanced and reloaded
 NEWS 16  OCT 30  CHEMLIST enhanced with new search and display field
 NEWS 17  NOV 03  JAPIO enhanced with IPC 8 features and functionality
 NEWS 18  NOV 10  CA/CAplus F-Term thesaurus enhanced
 NEWS 19  NOV 10  STN Express with Discover! free maintenance release Version
                  8.01c now available
 NEWS 20  NOV 20  CAS Registry Number crossover limit increased to 300,000 in
                  additional databases
 NEWS 21  NOV 20  CA/CAplus to MARPAT accession number crossover limit increased
                  to 50,000
 NEWS 22  DEC 01  CAS REGISTRY updated with new ambiguity codes
 NEWS 23  DEC 11  CAS REGISTRY chemical nomenclature enhanced
 NEWS 24  DEC 14  WPIDS/WPINDEX/WPIX manual codes updated
 NEWS 25  DEC 14  GBFULL and FRFULL enhanced with IPC 8 features and
                  functionality
 NEWS 26  DEC 18  CA/CAplus pre-1967 chemical substance index entries enhanced
                  with preparation role
 NEWS 27  DEC 18  CA/CAplus patent kind codes updated
 NEWS 28  DEC 18  MARPAT to CA/CAplus accession number crossover limit increased
                  to 50,000
 NEWS 29  DEC 18  MEDLINE updated in preparation for 2007 reload
 NEWS 30  DEC 27  CA/CAplus enhanced with more pre-1907 records

 NEWS EXPRESS  NOVEMBER 10 CURRENT WINDOWS VERSION IS V8.01c, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 25 SEPTEMBER 2006.

 NEWS HOURS    STN Operating Hours Plus Help Desk Availability
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 NEWS IPC8     For general information regarding STN implementation of IPC 8
 NEWS X25      X.25 communication option no longer available
 NEWS PRICE    STN 2007 Prices

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FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006

=> file uspatful
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     0.21       0.21

FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
CA INDEXING COPYRIGHT (C) 2006 AMERICAN CHEMICAL SOCIETY (ACS)
```

FILE COVERS 1971 TO PATENT PUBLICATION DATE: 28 Dec 2006 (20061228/PD)
FILE LAST UPDATED: 28 Dec 2006 (20061228/ED)
HIGHEST GRANTED PATENT NUMBER: US7155745
HIGHEST APPLICATION PUBLICATION NUMBER: US2006294631
CA INDEXING IS CURRENT THROUGH 28 Dec 2006 (20061228/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 28 Dec 2006 (20061228/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2006
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2006

=> s dengue
L1 3111 DENGUE

=> s l1 and 45AZ5
6 45AZ5
L2 6 L1 AND 45AZ5

=> s l2 and PDK-27
401 PDK
1938830 27
6 PDK-27
(PDK(W)27)
L3 6 L2 AND PDK-27

=> d l3,cbib,clm,1-6

L3 ANSWER 1 OF 6 USPATFULL on STN
2005:11907 Development of mutations useful for attenuating **dengue** viruses and chimeric **dengue** viruses.
Whitehead, Stephen S., Montgomery Village, MD, UNITED STATES
Murphy, Brian R., Bethesda, MD, UNITED STATES
Hanley, Kathryn A., Bethesda, MD, UNITED STATES
Blaney, Joseph E., Frederick, MD, UNITED STATES
US 2005010043 A1 20050113
APPLICATION: US 2003-719547 A1 20031121 (10)
PRIORITY: US 2001-293049P 20010522 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A flavivirus having a phenotype in which the viral genome is modified by the introduction of a mutation, singly or in combination, taken from the group consisting of the mutations of any of Table 1-37, preferably Table 37.

2. The flavivirus of claim 1, further comprising the Δ30 mutation.

3. The flavivirus of claim 1, wherein the flavivirus is a **dengue** virus type 1.

4. The flavivirus of claim 1, wherein the flavivirus is a **dengue** virus type 2.

5. The flavivirus of claim 1, wherein the flavivirus is a **dengue** virus type 3.

6. The flavivirus of claim 1, wherein the flavivirus is a **dengue** virus type 4.

7. The flavivirus of claim 1, wherein the flavivirus is a chimeric virus.

8. The chimeric virus of claim 7 having a **dengue** 1 backbone.

9. The chimeric virus of claim 7 having a **dengue** 2 backbone.

10. The chimeric virus of claim 7 having a **dengue** 3 backbone.

11. The chimeric virus of claim 7 having a **dengue** 4 backbone.

12. The flavivirus of claim 1, wherein the phenotype is temperature sensitivity in Vero cells or the human liver cell line HuH-7.

13. The flavivirus of claim 1, wherein the phenotype is host-cell restriction in mosquito cells or the human liver cell line HuH-7.

14. The flavivirus of claim 1, wherein the phenotype is host-cell adaptation for improved replication in Vero cells.

15. The flavivirus of claim 1, wherein the phenotype is attenuation in mice.

16. A pharmaceutical composition comprising a pharmacologically acceptable vehicle and a flavivirus according to any of claims 1-15.

17. A kit comprising a pharmaceutical composition according to claim 16 in a pack or dispenser device and instructions for administration.

18. A method of producing neutralizing antibodies against **dengue** virus comprising the administration of a therapeutically effective amount of a pharmaceutical composition comprising a pharmacologically acceptable vehicle and a flavivirus according to any of claims 1-15.

19. The method of claim 18, wherein administration is by subcutaneous, intradermal, or intramuscular injection.

20. A tetravalent vaccine comprising a pharmacologically acceptable vehicle and a flavivirus according to any of claims 1-15.

21. An live attenuated vaccine comprising a pharmacologically acceptable vehicle and a flavivirus according to any of claims 1-15.

22. The live attenuated vaccine of claim 21 in unit dosage form having from about 10^{2-109} plaque forming units (PFU)/ml.

23. An inactivated vaccine comprising a pharmacologically acceptable vehicle and ~~a flavivirus according to any of claims 1-15~~.

24. The inactivated vaccine of claim 23 in unit dosage form having from about 0.1 to 50 µg of E protein/ml.

25. A cDNA molecule encoding a flavivirus according to any of claims 1-15.

26. An RNA molecule encoding a flavivirus according to any of claims 1-15.

27. A method of preparing a flavivirus comprising (a) synthesizing full-length viral genomic RNA in vitro using a cDNA molecule that encodes a flavivirus according to any of claims 1-15; (b) transfecting cultured cells with the viral genomic RNA to produce virus; and (c) isolating the virus from the cultured cells.

28. A method of making a pharmaceutical composition comprising combining a pharmacologically acceptable vehicle and a flavivirus according to any of claims 1-15.

29. A method of identifying a mutation that restricts replication in human liver cells comprising (a) introducing mutations into a **dengue** virus genome to make mutant viruses; (b) screening the mutant viruses for a phenotype characterized by host-cell restriction in human liver cells; and (c) determining the genetic basis for the phenotype by direct sequence analysis of the virus genome.

30. A method of identifying a mutation that promotes growth in Vero cells comprising (a) introducing mutations into a **dengue** virus genome to make mutant viruses; (b) screening the mutant viruses for a phenotype characterized by host-cell adaptation for improved replication in Vero cells; and (c) determining the genetic basis for the phenotype by direct sequence analysis of the virus genome.

31. A method of assembling a menu of mutations for use in fine-tuning the attenuation and growth characteristics of recombinant **dengue** viruses comprising (a) introducing mutations into a **dengue** virus genome to make mutant viruses; (b) screening the mutant viruses for a phenotype characterized by temperature sensitivity in Vero cells or human liver cells, host cell restriction in mosquito cells or human liver cells, host-cell adaptation for improved replication in Vero cells, or attenuation in mice; (c) determining the genetic basis for the phenotype by direct sequence analysis of the virus genome; and (d)

performing multiple iterations of steps (a)-(c), whereby a menu of mutations is assembled.

32. The method of any of claims 29-30 further comprising introducing the mutation identified by said method into a recombinant **dengue** virus, and characterizing the resulting phenotype.

L3 ANSWER 2 OF 6 USPATFULL on STN
2003:285090 Multivalent **dengue** virus vaccine.
Eckels, Kenneth H., Rockville, MD, United States
Putnak, Joseph R., Silver Spring, MD, United States
Dubois, Doria R., Wheaton, MD, United States
Innis, Bruce L., Haverford, PA, United States
Hoke, Charles H., Columbia, MD, United States
Wellington, Sun, Rockville, MD, United States
Kanessa-thasan, Niranjan, Rockville, MD, United States
The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)
US 6638514 B1 20031028
APPLICATION: US 2000-535117 20000324 (9)
PRIORITY: US 2000-181724P 20000211 (60)
US 1999-126313P 19990326 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An immunogenic composition comprising two or more attenuated **dengue** viruses selected from the group consisting of a **dengue**-1 (DEN-1) virus having the sequence of DEN-1 strain **45AZ5** PDK-20 having the ATCC accession number VR-2648, a **dengue**-2 (DEN-2) virus having the sequence of DEN-2 strain S16803 PDK-50 having the ATCC accession number VR-2653, a **dengue**-3 (DEN-3) virus having the sequence of DEN-3 strain CH53489 PDK-20 having the ATCC accession number VR-2647, and a **dengue**-4 (DEN-4) virus having the sequence of DEN-4 strain 341750 PDK-20 having the ATCC accession number VR-2652, and a physiologically acceptable vehicle.

2. The immunogenic composition according to claim 1 which further comprises an adjuvant to enhance the immune response.

3. The immunogenic composition of claim 1, formulated in a dose of 10^2 to 10^6 PFU of attenuated virus.

4. A multivalent live attenuated **dengue** virus vaccine comprising any combination of **dengue** virus serotypes selected from the group consisting of: a **dengue**-1 (DEN-1) virus having the sequence of DEN-1 strain **45AZ5** PDK-20 having the ATCC accession number VR-2648, a **dengue**-2 (DEN-2) virus having the sequence of DEN-2 strain S 16803 PDK-50 having the ATCC accession number VR-2653, a **dengue**-3 (DEN-3) virus having the sequence of DEN-3 strain CH53489 PDK-20 having the ATCC accession number VR-2647, and a **dengue**-4 (DEN-4) virus having the sequence of DEN-4 strain 341750 PDK-20 having the ATCC accession number VR-2652.

5. The **dengue** virus vaccine of claim 4 wherein said **dengue** virus is produced in vertebrate cells.

6. The **dengue** virus vaccine of claim 5 wherein said cells are Vero cells.

7. The **dengue** virus vaccine of claim 4 wherein said **dengue**-1 virus is in the amount of 10^2 to 10^7 pfu/ml, said **dengue**-2 virus is in the amount of 10^2 to 10^7 pfu, said **dengue**-3 virus is in the amount of 10^2 to 10^7 pfu, and said **dengue**-4 virus is in the amount of 10^2 to 10^7 pfu/ml.

8. The **dengue** virus vaccine of claim 7 wherein said vaccine is administered subcutaneously.

9. An immunogenic composition comprising two or more attenuated **dengue** virus chosen from the group consisting of a **dengue**-1 (DEN-1) virus having the sequence of DEN-1 sawn **45AZ5 PDK-27** having the ATCC accession number PTA4810, a **dengue**-2 (DEN-2) virus having the sequence of DEN-2 strain S16803 PDK-SO having the ATCC accession number VR-2653, a **dengue**-3 (DEN-3) virus having the sequence of DEN-3 strain CH153489

PDK-20 having the ATCC accession number VR-2647, and a **dengue**-4 (DEN4) virus having the sequence of DEN-4 strain 341750 PDK6 having the ATCC accession number PTA4811, and a physiologically acceptable vehicle.

10. A multivalent live attenuated **dengue** virus vaccine comprising any combination of **dengue** virus serotypes selected from the group consisting of: a **dengue**-1 (DEN-1) virus having the sequence of DEN-1 strain **45AZ5 PDK-27** having the ATCC accession number PTA4810, a **dengue**-2 (DEN-2) virus having the sequence of DEN-2 strain S16803 PDK-50 having the ATCC accession number VR-2653, a **dengue**-3 (DEN-3) virus having the sequence of DEN-3 strain CH53489 PDK-20 having the ATCC accession number VR-2647, and a **dengue**-4 (DEN-4) virus having the sequence of DEN-4 stain 341750 PDK-6 having the ATCC accession number PTA-4811.

11. The vaccine of claim 10 wherein at least one virus os DEN-1 strain **45Az5 PDK-27** having the ATCC accessior number PTA-4810.

12. The vaccine of claim 10 wherein at least one virus is DEN-4 strain 341750 PDK-6 having the ATCC accessior number PTA-4811.

L3 ANSWER 3 OF 6 USPATFULL on STN
2003:234689 Adaptation of virus to vertebrate cells.
Eckels, Kenneth H., Rockville, MD, United States
Putnak, Joseph R., Silver Spring, MD, United States
Innis, Bruce L., Haverford, PA, United States
The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)
US 6613556 B1 20030902
APPLICATION: US 2000-534724 20000324 (9)
PRIORITY: US 1999-126316P 19990326 (60)
US 2000-182065P 20000211 (60)
DOCUMENT TYPE: Utility; GRANTED.
CLM What is claimed is:
1. A method for replicating **dengue** virus to a titer growth of at least 10^5 PFU/ml, wherein the **dengue** virus is selected from the group consisting of the **dengue**-1 strain identified as **45AZ5** PDK20 and given the ATCC accession no. VR-2648; the **dengue**-2 strain identified as S16803 PDK50 and given the ATCC accession no. VR-2653, the **dengue** 3 strain identified as CH53489 PDK20 and given the ATCC accession no. VR-2647, and the **dengue** 4 strain identified as 341750 PDK20 and given the ATCC accession no. VR-2652, comprising the step of infecting cells from a continuous epithelial or fibroblast cell line with a growth strain having a titer growth of at least 10^5 PFU/ml, wherein said continuous epithelial or fibroblast cell line lacks contaminating adventitious agents such that cells from said cell line are suitable for use in mammalian virus vaccine production.

2. The method of claim 1 wherein the **dengue** virus is chosen from the group consisting of: **dengue** 1, **dengue** 2, **dengue** 3, and **dengue** 4.

3. The method according to claim 2 wherein said **dengue** virus is attenuated.

4. The method of claim 1 wherein said cells are Vero cells.

5. The method of claim 4 wherein said Vero cells have a passage number of 20-190.

L3 ANSWER 4 OF 6 USPATFULL on STN
2003:81459 Attenuated **dengue**-4 virus vaccine.
Eckels, Kenneth H., Rockville, MD, United States
Putnak, Joseph R., Silver Spring, MD, United States
Dubois, Doria R., Wheaton, MD, United States
Innis, Bruce L., Haverford, PA, United States
Hoke, Charles H., Columbia, MD, United States
Vaughn, David, Silver Spring, MD, United States
The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)
US 6537557 B1 20030325
APPLICATION: US 2000-534726 20000324 (9)
PRIORITY: US 1999-126318P 19990326 (60)
US 2000-182068P 20000211 (60)

DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An immunogenic composition comprising an attenuated **dengue**-4 virus strain 341750 PDK-6, in a physiologically acceptable vehicle.

2. The immunogenic composition according to claim 1, which induces a **dengue**-4 specific immune response in individuals.

3. The immunogenic composition of claim 1, formulated in a dose of 10^4 to 10^5 PFU of attenuated virus.

L3 ANSWER 5 OF 6 USPATFULL on STN
2003:59949 Attenuated **dengue**-3 virus vaccine.
Eckels, Kenneth H., Rockville, MD, United States
Putnak, Joseph R., Silver Spring, MD, United States
Dubois, Doria R., Wheaton, MD, United States
Innis, Bruce L., Hayerford, PA, United States
Hoke, Charles H., Columbia, MD, United States
Vaughn, David, Silver Spring, MD, United States
The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)
US 6528065 B1 20030304
APPLICATION: US 2000-535684 20000324 (9)
PRIORITY: US 2000-182063P 20000211 (60)
US 1999-126311P 19990326 (60)
DOCUMENT TYPE: Utility; GRANTED.
CLM What is claimed is:
1. An immunogenic composition comprising, in a physiologically acceptable vehicle, at least one attenuated **dengue**-3 virus having the sequence of the virus designated ATCC accession number VR-2647.

2. The immunogenic composition according to claim 1, which induces a **dengue**-3 specific immune response in individuals.

3. The immunogenic composition of claim 1, formulated in a dose of 10^4 to 10^5 PFU of attenuated virus.

L3 ANSWER 6 OF 6 USPATFULL on STN
2003:26150 Attenuated **dengue**-2 virus vaccine.
Eckels, Kenneth H., Rockville, MD, United States
Putnak, Joseph R., Silver Spring, MD, United States
Dubois, Doria R., Wheaton, MD, United States
Innis, Bruce L., Haverford, PA, United States
Hoke, Charles H., Columbia, MD, United States
Vaughn, David, Silver Spring, MD, United States
Henchai, Erik A., Rockville, MD, United States
Kanesa-thasan, Niranian, Rockville, MD, United States
The United States of America as represented by the Secretary of the Army, Washington, DC, United States (U.S. government)
US 6511667 B1 20030128
APPLICATION: US 2000-534725 20000324 (9)
PRIORITY: US 1999-126319P 19990326 (60)
US 2000-182067P 20000211 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. An immunogenic composition comprising, in a physiologically acceptable vehicle, at least one attenuated **dengue**-2 virus having the sequence of the virus designated ATCC accession number VR-2653.

2. The immunogenic composition according to claim 1, which induces a **dengue**-2 specific immune response in individuals.

3. The immunogenic composition of claim 1, formulated in a dose of 10^4 to 10^5 PFU of attenuated virus.

=> d his

(FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

```
     FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1          3111 S DENGUE
L2             6 S L1 AND 45AZ5
L3             6 S L2 AND PDK-27

=> s l1 and S16803
            14 S16803
L4          14 L1 AND S16803

=> s l4 not l2
L5           9 L4 NOT L2

=> s l5 and PDK-50
           401 PDK
       2673566 50
             7 PDK-50
                 (PDK(W)50)
L6           1 L5 AND PDK-50

=> d l6,cbib,clm

L6   ANSWER 1 OF 1  USPATFULL on STN
2004:146867 Recombinant dimeric envelope vaccine against flaviviral infection.
    Peters, Iain D., Bozeman, MT, United States
    Coller, Beth-Ann G., Woluwe Saint Lambert, BELGIUM
    McDonell, Michael, Bogart, GA, United States
    Ivy, John M., College Station, TX, United States
    Harada, Kent, Honolulu, HI, United States
    Hawaii Biotechnology Group, Inc., Aiea, HI, United States (U.S.
    corporation)
    US 6749857 B1 20040615
    APPLICATION: US 1999-376463 19990818 (9)
    DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A vaccine that generates a protective, neutralizing antibody response
       to a Flavivirus in a murine host, wherein said vaccine comprises a
       therapeutically effective amount of a dimeric 80%E, said dimeric 80%E
       having been secreted as a recombinantly produced protein from Drosophila
       Schneider cells, wherein 80%E represents the N-terminal 80% portion of
       the protein from residue 1 to residue 395.

       2. The vaccine of claim 1 wherein said dimeric 80%E is selected from the
       group consisting of: linked 80%E dimer; 80%E ZipperI; 80%E ZipperII; and
       80%E Bundle.

       3. The vaccine of claim 2 wherein the linked 80%E dimer is a truncated
       envelope protein of serotype DEN-1.

       4. The vaccine of claim 2 wherein the linked 80%E dimer is a truncated
       envelope protein of serotype DEN-2.

       5. The vaccine of claim 1 wherein the linked 80%E dimer is a truncated
       envelope protein of serotype DEN-3.

       6. The vaccine of claim 1 wherein the linked 80%E dimer is a truncated
       envelope protein of serotype DEN-4.

       7. A multivalent vaccine that generates a protective, neutralizing
       antibody response to a Flavivirus in a murine host, wherein said vaccine
       comprises a therapeutically effective amount of a first dimeric 80%E
       product of one flaviviral serotype; a second dimeric 80%E product of a
       second flaviviral serotype; a third dimeric 80%E product of a third
       flaviral serotype; and a fourth dimeric 80%E product of a fourth
       flaviviral serotype; wherein all dimeric 80%E products have been
       secreted as recombinantly produced protein from a Drosophila Schneider
       cell, wherein 80%E is the N-terminal 80% of the protein from residue 1
       to 395.

       8. The vaccine of claim 7 wherein said dimeric 80%E products are
       envelope proteins of serotypes selected from the group consisting of:
       DEN-1; DEN-2; DEN-3; and DEN-4.

       9. The vaccine of claim 1 wherein said Flavivirus is a dengue virus.
```

10. The vaccine of claim 2 wherein said Flavivirus is a **dengue** virus.

11. The vaccine of claim 7 wherein said Flavivirus is a **dengue** virus.

12. An immunogenic polypeptide comprising a dimeric 80%E, said dimeric 80%E having been secreted as a recombinantly produced protein from Drosophila Schneider cells, wherein 80%E represents the N-terminal 80% of the protein from residue 1 to residue 395.

13. The immunogenic polypeptide of claim 12 wherein said dimeric 80%E is selected from the group consisting of: linked 80%E dimer, 80%E ZipperI; 80%E ZipperII; and 80%E bundle.

14. The immunogenic polypeptide of claim 13 wherein the linked 80%E dimer is a truncated envelope protein which is at least one member selected from the group consisting of serotype DEN-1, serotype DEN-2, serotype DEN-3, and serotype DEN-4.

15. An immunogenic composition that generates a protective, neutralizing antibody response to a Flavivirus in a murine host, comprising the immunogenic polypeptide defined in claim 12 and a physiologically acceptable carrier.

16. The immunogenic composition defined in claim 15 further comprising an adjuvant.

17. The immunogenic composition defined in claim 15 wherein said adjuvant is Iscomatrix.

18. The immunodiagnostic for the detection of Flavivirus comprising the immunogenic polypeptide defined in claim 12.

19. A multivalent immunodiagnostic for the detection of Flavivirus comprising at least two of the immunogenic polypeptides defined in claim 12 of at least two flaviviral serotypes.

20. An immunodiagnostic kit for the detection of Flavivirus in a test subject comprising a) the immunogenic polypeptide defined in claim 12; b) a suitable support phase coated with dimeric 80%E; and c) labeled antibodies immunoreactive to antibodies from said test subject.

21. An immunodiagnostic kit for the detection of Flavivirus in a test subject comprising a) the multivalent immunodiagnostic polypeptide defined in claim 19; b) a suitable support phase coated with dimeric 80%E; and c) labeled antibodies immunoreactive to antibodies from said test subject.

```
=> d his

     (FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

     FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1          3111 S DENGUE
L2             6 S L1 AND 45AZ5
L3             6 S L2 AND PDK-27
L4            14 S L1 AND S16803
L5             9 S L4 NOT L2
L6             1 S L5 AND PDK-50

=> s l1 and CH53489
            12 CH53489
L7          12 L1 AND CH53489

=> s l7 not (l3 or l6)
L8           7 L7 NOT (L3 OR L6)

=> s l8 and PDK-20
           401 PDK
       3717438 20
             6 PDK-20
                 (PDK(W)20)
L9           0 L8 AND PDK-20
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```
=> s l1 and 341750
             9 341750
L10          9 L1 AND 341750

=> s l10 not (l3 or l6)
L11          4 L10 NOT (L3 OR L6)

=> d l11,cbib,clm,1-4

L11  ANSWER 1 OF 4  USPATFULL on STN
2004:327404 Tetravalent Dengue vaccines.
    Guirakhoo, Farshad, Melrose, MA, UNITED STATES
    US 2004259224 A1 20041223
    APPLICATION: US 2003-452610  A1  20030602 (10)
    PRIORITY: US 2002-385013P  20020531 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A method of inducing an immune response to the four serotypes of
       dengue virus in a patient, the method comprising administering to the
       patient a vaccine comprising:  a chimeric flavivirus comprising the
       capsid and non-structural proteins of Yellow Fever virus and the
       pre-membrane and envelope proteins of Dengue-1 virus;  a chimeric
       flavivirus comprising the capsid and non-structural proteins of Yellow
       Fever virus and the pre-membrane and envelope proteins of Dengue-2
       virus;  a chimeric flavivirus comprising the capsid and non-structural
       proteins of Yellow Fever virus and the pre-membrane and envelope
       proteins of Dengue-3 virus; and  a chimeric flavivirus comprising the
       capsid and non-structural proteins of Yellow Fever virus and the
       pre-membrane and envelope proteins of Dengue-4 virus.

       2. The method of claim 1, wherein all four chimeras are administered at
       equivalent concentrations.

       3. The method of claim 2, wherein each chimera is administered at a
       concentration of 5log10 PFU.

       4. The method of claim 2, wherein each chimera is administered at a
       concentration of 4log10 PFU.

       5. The method of claim 1, wherein the Dengue-1 and Dengue-2 chimeras
       are administered at an amount that is greater than that of the
       Dengue-3 and Dengue-4 chimeras.

       6. The method of claim 5, wherein said Dengue-1 and Dengue-2
       chimeras are administered at 5logio PFU and said Dengue-3 and
       Dengue-4 chimeras are administered at 4log10 PFU.

       7. The method of claim 5, wherein said Dengue-1 and Dengue-2
       chimeras are administered at 5log10 PFU and said Dengue-3 and
       Dengue-4 chimeras are administered at 3log10 PFU.

       8. The method of claim 5, wherein said Dengue-1 and Dengue-2
       chimeras are administered at 4log10 PFU and said Dengue-3 and
       Dengue-4 chimeras are administered at 3log10 PFU.

       9. The method of claim 1, wherein said patient does not have, but is at
       risk of developing, Dengue infection.

       10. The method of claim 1, wherein said patient has Dengue infection.

       11. A vaccine composition comprising:  a chimeric flavivirus comprising
       the capsid and non-structural proteins of Yellow Fever virus and the
       pre-membrane and envelope proteins of Dengue-1 virus;  a chimeric
       flavivirus comprising the capsid and non-structural proteins of Yellow
       Fever virus and the pre-membrane and envelope proteins of Dengue-2
       virus;  a chimeric flavivirus comprising the capsid and non-structural
       proteins of Yellow Fever virus and the pre-membrane and envelope
       proteins of Dengue-3 virus; and  a chimeric flavivirus comprising the
       capsid and non-structural proteins of Yellow Fever virus and the
       pre-membrane and envelope proteins of Dengue-4 virus.

       12. The composition of claim 11, wherein all four chimeras are present
       in said composition in equivalent concentrations.
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13. The composition of claim 12, wherein each chimera is present at a concentration of $5\log_{10}$ PFU.

14. The composition of claim 12, wherein each chimera is present at a concentration of $4\log_{10}$ PFU.

15. The composition of claim 11, wherein the **Dengue**-1 and **Dengue**-2 chimeras are present in an amount that is greater than that of the **Dengue**-3 and **Dengue**-4 chimeras.

16. The composition of claim 15, wherein said **Dengue**-1 and **Dengue**-2 chimeras are present at $5\log_{10}$ PFU and said **Dengue**-3 and **Dengue**-4 chimeras are present at $4\log_{10}$ PFU.

17. The composition of claim 15, wherein said **Dengue**-1 and **Dengue**-2 chimeras are present at $5\log_{10}$ PFU and said **Dengue**-3 and **Dengue**-4 chimeras are present at $3\log_{10}$ PFU.

18. The composition of claim 15, wherein said **Dengue**-1 and **Dengue**-2 chimeras are present at $4\log_{10}$ PFU and said **Dengue**-3 and **Dengue**-4 chimeras are present at $3\log_{10}$ PFU.

L11 ANSWER 2 OF 4 USPATFULL on STN
2004:235351 Flavivirus detection and quantification assay.
Houng, Huo-Shu H., Burtonsville, MD, United States
Kanesa-Thasan, Niranjan, Rockville, MD, United States
U.S. Army Medical Research & Materiel Command, Ft. Detrick, MD, United States (U.S. corporation)
US 6793488 B1 20040921
APPLICATION: US 2000-551161 20000414 (9)
PRIORITY: US 1999-153685P 19990914 (60)
US 1999-129713P 19990416 (60)
DOCUMENT TYPE: Utility; GRANTED.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A composition suitable for use in a process involving DNA amplification comprising DNA segments of 19-36 nucleotides in length which have sequences selected from: Serotype-specific Upstream Primers (5) DV1-1U 5'-GAT-CAA-GCT-TACA-CCA-GGG-GAA-GCT-GTA-TCC-TGG-3' (SEQ ID NO 4), DV2-2U 5'-GAT-CAA-GCT-TAAG-GTC-AGA-TGA-AGC-TGT-AGT-CTC-3' (SEQ ID NO 5), DV3-1U 5'-GAT-CAA-GCT-TAGC-ACT-GAG-GGA-AGC-TGT-ACC-TCC-3' (SEQ ID NO 6), DV4-1U 5'-GAT-CAA-GCT-TAAG-CCA-GGA-GGA-AGC-TGT-ACT-CCT-3' (SEQ ID NO 7), and JE.F2-5'-CAAGCCCCCTCGAAGCTGT-3' (SEQ ID NO 13); Serotype-specific Fluorescent probes (4) DV1-P1 5'-CTG-TCT-DTA-CAG-CAT-CAT-TCC-AGG-CA-3' (SEQ ID NO 8), DV4-P1 5'-CTG-TCT-CTG-CAA-CAT-CAA-TCC-AGG-CA-3' (SEQ ID NO 9), DV2-P1 5'-CTG-TCT-CCT-CAG-CAT-CAT-TCC-AGG-CA-3' (SEQ ID NO 1), and JE.P1 5'-TCTGCTCTATCTCAACATCAGCTACTAGGCACAGA-3' (SEQ ID NO 12); and Serotype-specific Down-stream Primer (3) DV4-1L 5'-CAA-TCC-ATC-TTG-CGG-CGC-TCT-3' (SEQ ID NO 10), DV2-1L 5'-GAT-CGA-ATT-CCAT-TCC-ATT-TTC-TGG-CGT-TCT-3' (SEQ ID NO 11), and JE.R382 5'-CACCAGCTACATACTTCGGCG-3' (SEQ ID NO 14); or the complement thereof, wherein the composition contains a) at least one of said serotype-specific upstream primers and one of said serotype-specific down stream primers or b) one of said serotype-specific fluorescent probes.

2. The isolated DNA segments of claim 1 wherein said segments are probes and are labeled.

3. The probe of claim 2 wherein the label is fluorescent.

4. The probe of claim 2 wherein the label is a quencher.

5. The probe of claim 2 wherein the segment is labeled at both the 3' and 5' end, respectively, where one label is a quencher and the other is a fluorescent.

6. A PCR-based diagnostic kit for detecting or quantitating a flavivirus serotype comprising: isolated DNA segments of 19-36 nucleotides which have sequences selected from: Serotype-specific Upstream Primers (5) DV1-1U 5'-GAT-CAA-CT-TACA-CCA-GGG-GAA-GCT-GTA-TCC-TGG-3' (SEQ ID NO 4), DV2-2U 5'-GAT-CAA-GCT-TAAG-GTC-AGA-TGA-AGC-TGT-AGT-CTC-3' (SEQ ID NO 5), DV3-1U 5'-GAT-CAA-GCT-TAGC-ACT-GAG-GGA-AGC-TGT-ACC-TCC-3' (SEQ ID NO 6), DV4-1U 5'-GAT-CAA-GCT-TAAG-CCA-GGA-GGA-AGC-TGT-ACT-CCT-3' (SEQ ID NO 7),

and JE.F214 5'-CAAGCCCCCTCGAAGCTGT-3' (SEQ ID NO 13); Serotype-specific Fluorescent probes (4) DV1-P1 5'-CTG-TCT-DTA-CAG-CAT-CAT-TCC-AGG-CA-3' (SEQ ID NO 8), DV4-P1 5'-CTG-TCT-CTG-CAA-CAT-CAA-TCC-AGG-CA-3' (SEQ ID NO 9), DV2-P1 5'-CTG-TCT-CCT-CAG-CAT-CAT-TCC-AGG-CA-3' (SEQ ID NO 1), and JE.P1 5'-TCTGCTCTATCTCAACATCAGCTACTAGGCACAGA-3' (SEQ ID NO 12); and Serotype-specific Down-stream Primer (3) DV4-1L 5'-CAA-TCC-ATC-TTG-CGG-CGC-TCT-3' (SEQ ID NO 10), DV2-1L 5'-GAT-CGA-ATT-CCAT-TCC-ATT-TTC-TGG-CGT-TCT-3' (SEQ ID NO 11), and JE.R382 5'-CACCAGCTACATACTTCGGCG-3' (SEQ ID NO 14); or the complement thereof, wherein the kit contains a) at least one of said serotype-specific upstream primers and one of said serotype-specific down stream primers or b) one of said serotype-specific fluorescent probes.

7. The kit of claim 6 wherein said segments are labeled probes.

8. The kit of claim 7 wherein the label is fluorescent.

9. The kit of claim 7 wherein the label is a quencher.

10. The kit of claim 6 wherein the segment is labeled at both the 3' and 5' end, respectively, where one label is a quencher and the other is a fluorescent.

11. A method for detecting or quantifying one or more species of flavivirus contained in sample comprising the steps of: i) collecting a sample suspected of containing a flavivirus; ii) preparing said sample for PCR amplification; iii) adding to said prepared sample, PCR reagents including both probes and primer pairs wherein the probes and primers in the primer pair consist of 19-36 nucleotides in lenght and contain any one of the following, Serotype-specific Upstream Primers (5) DV1-1U 5'-GAT-CAA-GCT-TACA-CCA-GGG-GAA-GCT-GTA-TCC-TGG-3' (SEQ ID NO 4), DV2-2U 5'-GAT-CAA-GCT-TAAG-GTC-AGA-TGA-AGC-TGT-AGT-CTC-3' (SEQ ID NO 5), DV3-1U 5' -GAT-CAA-GCT-TAGC-ACT-GAG-GGA-AGC-TGT-ACC-TCC-3' (SEQ ID NO 6), DV4-1U 5'-GAT-CAA-GCT-TAAG-CCA-GGA-GGA-AGC-TGT-ACT-CCT-3' (SEQ ID NO 7), and JE.F214 5'-CAAGCCCCCTCGAAGCTGT-3' (SEQ ID NO 13); Serotype-specific Fluorescent probes (4) DV1-P1 5'-CTG-TCT-DTA-CAG-CAT-CAT-TCC-AGG-CA-3' (SEQ ID NO 8), DV4-P1 5'-CTG-TCT-CTG-CAA-CAT-CAA-TCC-AGG-CA-3' (SEQ ID NO 9), DV2-P1 5'-CTG-TCT-CCT-CAG-CAT-CAT-TCC-AGG-CA-3' (SEQ ID NO 1), and JE.P1 5'-TCTGCTCTATCTCAACATCAGCTACTAGGCACAGA-3' (SEQ ID NO 12); and Serotype-specific Down-stream Primer (3) DV4-1L 5'-CAA-TCC-ATC-TTG-CGG-CGC-TCT-3' (SEQ ID NO 10), DV2-1L 5'-GAT-CGA-ATT-CCAT-TCC-ATT-TTC-TGG-CGT-TCT-3' (SEQ ID NO 11), and JE.R382 5'-CACCAGCTACATACTTCGGCG-3' (SEQ ID NO 14); or the complement thereof, wherein a) the primer pairs comprise at least one of said serotype-specific upstream primers and one of said serotype-specific down stream primers or b) at a least one probe is one of said serotype-specific fluorescent probes; iv) maintaining the sample under conditions suitable for amplification; v) detecting or quantifying one or more of the flavivirus species.

12. The method of claim 11 wherein said serotype-specific fluorescent probes of step (iii) are labeled with a fluorescent label.

13. The method of claim 11 wherein said serotype-specific fluorescent probes of step (iii) are labeled with a quencher.

14. The method of claim 11 wherein the segment is labeled at both the 3' and 5' end, respectively, where one label is a quencher and the other is a fluorescent.

15. The method of claim 11 wherein said flavivirus is **Dengue**.

16. The method of claim 15 wherein said **Dengue** virus is **Dengue** 1, 2, 3, or 4.

17. A method for detecting or quantifying **dengue** virus Serotype(s) comprising i) contacting a sample suspected of containing a flavivirus with PCR reagents, including at least two PCR primers selected from the following groups: Serotype-specific Upstream Primers (5) DV1-1U 5'-GAT-CAA-GCT-TACA-CCA-GGG-GAA-GCT-GTA-TCC-TGG-3' (SEQ ID NO 4), DV2-2U 5' -GAT-CAA-GCT-TAAG-GTC-AGA-TGA-AGC-TGT-AGT-CTC-3' (SEQ ID NO 5), DV3-1U 5' -GAT-CAA-GCT-TAGC-ACT-GAG-GGA-AGC-TGT-ACC-TCC-3' (SEQ ID NO 6), DV4-1U 5'-GAT-CAA-GCT-TAAG-CCA-GGA-GGA-AGC-TGT-ACT-CCT-3' (SEQ ID NO 7), and JE.F214 5'-CAAGCCCCCTCGAAGCTGT-3' (SEQ ID NO 13); Serotype-specific Down-stream Primer (3) DV4-1L 5'-CAA-TCC-ATC-TTG-CGG-CGC-TCT-3' (SEQ ID NO 10), DV2-1L 5'-GAT-CGA-ATT-CCAT-TCC-ATT-TTC-TGG-

CGT-TCT-3' (SEQ ID NO 11), and JE.R382 5'-CACCAGCTACATACTTCGGCG-3' (SEQ ID NO 14), or the complement thereof, wherein the primer pairs comprise at least one of said serotype specific upstream primers and one of said serotype specific down stream primers, and a polymerase enzyme, and an oligonucleotide probe selected from the following group: Serotype-specific fluorescent probes (4) DV1-P1 5'-CTG-TCT-DTA-CAG-CAT-CAT-TCC-AGG-CA-3' (SEQ ID NO 8), DV4-P1 5'-CTG-TCT-CTG-CAA-CAT-CAA-TCC-AGG-CA-3' (SEQ ID NO 9), DV2-P1 5'-CTG-TCT-CCT-CAG-CAT-CAT-TCC-AGG-CA-3' (SEQ ID NO 1), and JE.P1 5'-TCTGCTCTATCTCAACATCAGCTACTAGGCACAGA-3' (SEQ ID NO 12), or the complement thereof, wherein at least one of said oligonucleotide probes is a serotype specific fluorescent probe, and wherein a fluorescer molecule attached to a first end of the oligonucleotide probe and a quencher molecule attached to a second end of the oligonucleotide probe such that the quencher molecule substantially quenches the fluorescer molecule whenever the oligonucleotide probe is in the free stranded state and such that the fluorescer is substantially unquenched whenever the oligonucleotide probe is hybridized to the target nucleic acid; a 5' end which is rendered impervious to digestion by the 5'→3' exonuclease activity of a polymerase; and a 3' end which is rendered impervious to the 5'→3' extension activity of the polymerase; and ii) subjecting the sample, oligonucleotide probe, and the PCR reagents to thermal cycling, including a polymerization step, the thermal cycling being sufficient to amplify the target nucleic acid specified by the PCR reagents.

18. The method of claim 17 further comprising the step of measuring the extent of fluorescence quenching of the oligonucleotide probe, such measurement being performed subsequent to thermocycling and at a probe hybridization temperature.

19. The method of claim 17 further comprising the step of measuring the extent of fluorescence quenching of the oligonucleotide probe at a probe hybridization temperature in a manner which locates the probe within the individual cells originally containing the target nucleic acid sequence.

20. The method of claim 17 wherein the sample, the PCR reagents, and the oligonucleotide probe are located in a containment assembly.

21. The method of claim 17 wherein the probe hybridization temperature is less than or equal to the temperature of the polymerization step of the thermocycling.

L11 ANSWER 3 OF 4 USPATFULL on STN
2003:134595 Compositions and methods for treating hemorrhagic virus infections and other disorders.
Fredeking, Terry M., Bedford, TX, UNITED STATES
Ignatyev, George M., Koltsovo, RUSSIAN FEDERATION
US 2003092684 A1 20030515
APPLICATION: US 2002-38557 A1 20020103 (10)
PRIORITY: US 1999-198210P 19990427 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:
1. A method of treating a disease or disorder, comprising: administering a tetracycline or tetracycline-like compound, whereby the disease or disorder is treated or prevented, and wherein the disease, condition or disorder is selected from the group consisting of multiple sclerosis, rheumatoid arthritis, acute cardiovascular events, cachexia, inflammatory bowel disease, polytrauma and Crohn's disease.

2. The method of claim 1, wherein the tetracycline compound is selected from the group consisting of chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline and tetracycline.

3. The method of claim 1, wherein the disease, condition or disorder is multiple sclerosis.

4. The method of claim 1, wherein the disease, condition or disorder is a flare-up or acute phase of multiple sclerosis.

5. The method of claim 3, wherein the tetracycline compound is selected from the group consisting of chlortetracycline, demeclocycline,

doxycycline, methacycline, minocycline, oxytetracycline and tetracycline.

6. The method of claim 1, wherein the tetracycline compound is selected from the group consisting of 4-dedimethylaminotetracycline, 4-dedimethylamino-5-oxytetracycline, 4-dedimethylamino-7-chlortetracycline, 4-hydroxy-4-dedimethylaminotetracycline, 5a, 6-anhydro-4-hydroxy-4-dedimethylaminotetracycline, 6α-deoxy-5-hydroxy-4-dedimethylaminotetracycline, 6-demethyl-6-deoxy-4-dedimethylaminotetracycline, 4-dedimethylamino-12a-deoxytetracycline, 4-dedimethylamino-11-hydroxy-12a-deoxytetracycline, 12a-deoxy-4-deoxy-4-dedimethylaminotetracycline, 6a-deoxy-5-hydroxy-4-dedimethylaminodoxycycline, 12a,4a-anhydro-4-dedimethylaminotetracycline, 7-dimethylamino-6-demethyl-6-deoxy-4-dedimethylaminotetracycline, 6a-benzylthiomethylenetetracycline, 2-nitrilo analogs of tetracycline (tetracyclinonitrile), mono-N-alkylated amide of tetracycline, 6-fluoro-6-demethyltetracycline, 11 a-chlortetracycline, tetracycline pyrazole, 12a-deoxytetracycline, 4-de(dimethylamino)tetracycline (CMT-1), tetracyclinonitrile (CMT-2), 6-demethyl-6-deoxy-4--de(dimethylamino)tetracycline (CMT-3), 7-chloro-4-de(dimethylamino)tetracycline (CMT-4), tetracycline pyrazole (CMT-5), 4-hydroxy-4-de(dimethylamino)tetracycline (CMT-6), 4-de(dimethylamino)-12α-deoxytetracycline (CMT-7), 6-deoxy-5α-hydroxy-4-de(dimethylamino)tetracycline (CMT-8), 4-de(dimethylamino)-12α-deoxyanhydrotetracycline (CMT-9), 4-de(dimethylamino)minocycline (CMT-10), 5-ozytetracycline, 7-chlortetracycline, 6-deoxy-5-oxytetracycline, 6-deoxytetracycline, 6-deoxy-6-demethyltetracycline, 7-bromotetracycline, 6-demethyl-7-chlortetracycline, 6-demethyltetracycline, 6-methylenetetracycline, 11a-chloro-6-methylenetetracycline, 6-methylene-5-oxytetracycline and 11a-chloro-6-methylene-5-oxytetracycline.

7. The method of claim 3, wherein the tetracycline compound is selected from the group consisting of 4-dedimethylaminotetracycline, 4-dedimethylamino-5-oxytetracycline, 4-dedimethylamino-7-chlortetracycline, 4-hydroxy-4-dedimethylaminotetracycline, 5a,6-anhydro-4-hydroxy-4-dedimethylaminotetracycline, 6α-deoxy-5-hydroxy-4-dedimethylaminotetracycline, 6-demethyl-6-deoxy-4-dedimethylaminotetracycline, 4-dedimethylamino-12a-deoxytetracycline, 4-dedimethylamino-11 -hydroxy-12a-deoxytetracycline, 12a-deoxy-4-deoxy-4-dedimethylaminotetracycline, 6α-deoxy-5-hydroxy-4-dedimethylaminodoxycycline, 12a,4a-anhydro-4-dedimethylaminotetracycline, 7-dimethylamino-6-demethyl-6-deoxy-4-dedimethylaminotetracycline, 6a-benzylthiomethylenetetracycline, 2-nitrilo analogs of tetracycline (tetracyclinonitrile), mono-N-alkylated amide of tetracycline, 6-fluoro-6-demethyltetracycline, 11a-chlortetracycline, tetracycline pyrazole, 12a-deoxytetracycline, 4-de(dimethylamino)tetracycline (CMT-1), tetracyclinonitrile (CMT-2), 6-demethyl-6-deoxy-4--de(dimethylamino)tetracycline (CMT-3), 7-chloro-4-de(dimethylamino)tetracycline (CMT-4), tetracycline pyrazole (CMT-5), 4-hydroxy-4-de(dimethylamino)tetracycline (CMT-6), 4-de(dimethylamino)-12α-deoxytetracycline (CMT-7), 6-deoxy-5α-hydroxy-4-de(dimethyl-amino)tetracycline (CMT-8), 4-de(dimethylamino)-12α-deoxyanhydrotetracycline (CMT-9), 4-de(dimethylamino)minocycline (CMT-10), 5-ozytetracycline, 7-chlortetracycline, 6-deoxy-5-oxytetracycline, 6-deoxytetracycline, 6-deoxy-6-demethyltetracycline, 7-bromotetracycline, 6-demethyl-7-chlortetracycline, 6-demethyltetracycline, 6-methylenetetracycline, 11a-chloro-6-methylenetetracycline, 6-methylene-5-oxytetracycline and 11a-chloro-6-methylene-5-oxytetracycline.

L11 ANSWER 4 OF 4 USPATFULL on STN
2002:149120 Compositions and methods for treating hemorrhagic virus infections and other disorders.
Fredeking, Terry M., Bedford, TX, UNITED STATES
Ignatyev, George M., Koltsovo, RUSSIAN FEDERATION
US 2002077276 A1 20020620
APPLICATION: US 2001-840707 A1 20010423 (9)
PRIORITY: US 1999-198210P 19990427 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM What is claimed is:

1. A method of treating a disease, condition or disorder, comprising: administering blood or a soluble-receptor containing fraction thereof to a mammal suffering from an acute inflammatory condition, wherein prior to administration the blood or fraction thereof has been contacted with tetracycline or a tetracycline-like compound, whereby the level of a pre-selected cytokine receptor in the blood is at least three-fold higher than level of the receptors prior to contacting with the tetracycline or tetracycline-like compound.

2. The method of claim 1, wherein the cytokine receptor is a tumor necrosis factor (TNF) receptor and/or an interleukin-1 receptor (IL-1R).

3. The method of claim 1, wherein the disease, condition or disorder is selected from the group consisting of acute inflammatory conditions associated with viral hemorrhagic diseases, parasitic diseases, bacterial infections, sepsis, cachexia, autoimmune disorders, acute cardiovascular events, chronic myelogenous leukemia and transplanted bone marrow-induced graft-versus-host disease, septic shock, immune complex-induced colitis, cerebrospinal fluid inflammation, autoimmune disorders, multiple sclerosis; inflammatory responses associated with trauma; systemic inflammatory response syndrome (SIRS), adult respiratory distress syndrome (ARDS), acute liver failure, inflammatory bowel disease and Crohn's disease.

4. The method of claim 1, wherein the disease, condition or disorder is selected from viral hemorrhagic diseases and bacterial infections.

5. The method of claim 1, wherein the contacting with tetracycline or a tetracycline-like compound is effected by administering the tetracycline or tetracycline-like compound to the donor of the blood.

6. The method of ~~claim 1, wherein the mammal has a viral hemorrhagic~~ disease.

7. A method for treating or preventing a viral hemorrhagic disease, comprising administering an effective amount of a tetracycline or tetracycline-like compound, whereby the viral hemorrhagic disease is treated or prevented.

8. The method of claim 7, further comprising administering a blood-derived composition, wherein: the composition is produced by i) obtaining blood from a mammalian donor and measuring the level of a cytokine antagonist or cytokine receptor in the blood; and ii) administering to the mammalian donor or contacting blood from the donor with a tetracycline or tetracycline-like compound(s) in an amount sufficient and for a time sufficient to result in a three-fold increase in the measured cytokine antagonist or receptor; and the composition is administered simultaneously, subsequently or before administration of the tetracycline or tetracycline-like compound.

9. The method of claim 7, further comprising administering an anti-hemorrhagic viral treatment or agent to the mammal.

10. A combination, comprising: a) a tetracycline compound; and b) an anti-hemorrhagic virus treatment or agent.

11. The combination of claim 10, wherein the tetracycline compound and the anti-hemorrhagic virus agent are formulated in a single pharmaceutical composition or each formulated in a separate pharmaceutical compositions.

12. The combination of claim 10, wherein the tetracycline compound is selected from the group consisting of chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline and tetracycline.

13. The combination of claim 10, wherein the hemorrhagic virus is a Bunyaviridae, a Filoviridae, a Flaviviridae, or an Arenaviridae virus.

14. The combination of claim 10, wherein the anti-hemorrhagic virus agent inhibits interleukin-1 (IL-1) and/or tumor necrosis factor (TNF).

15. The combination of claim 14, wherein the agent that inhibits IL-1 is selected from the group consisting of anti-IL-1 antibodies, anti-IL-1 receptor antibodies, IL-1 receptor antagonists, IL-1 production

inhibitors, IL-1 receptor production inhibitors, and IL-1 releasing inhibitors.

16. The combination of claim 14, wherein the TNF inhibitor is selected from the group consisting of an anti-TNF antibody, an anti-TNF receptor antibody, a TNF receptor antagonist, a TNF production inhibitor, a TNF receptor production inhibitor and a TNF releasing inhibitor.

17. The combination of claim 10, wherein the anti-viral-hemorrhagic agent is selected from the group consisting of an anti-viral vaccine, an anti-viral antibody, a viral-activated immune cell and a viral-activated immune serum.

18. The method of claim 9, wherein the mammal is a human.

19. The method of claim 18, wherein the tetracycline compound is selected from the group consisting of chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline and tetracycline.

20. The method of claim 9, wherein the anti-viral hemorrhagic treatment comprises administering an effective amount of an anti-viral-hemorrhagic agent.

21. The method of claim 20, wherein the tetracycline compound and the anti-viral-hemorrhagic agent are administered sequentially.

22. The method of claim 21, wherein the tetracycline compound and the anti hemorrhagic virus treatment are co-administered.

23. The method of claim 22, wherein the tetracycline compound and the anti-viral-hemorrhagic agent are administered in the same composition.

24. The method of claim 9, wherein the anti-hemorrhagic virus agent inhibits interleukin-1 (IL-1) and/or tumor necrosis factor (TNF).

25. The method of claim 24, wherein the agent that inhibits IL-1 is selected from the group consisting of anti-IL-1 antibodies, anti-IL-1 receptor antibodies, IL-1 receptor antagonists, IL-1 production inhibitors, IL-1 receptor production inhibitors, and IL-1 releasing inhibitors.

26. The method of claim 25, wherein the TNF inhibitor is selected from the group consisting of an anti-TNF antibody, an anti-TNF receptor antibody, a TNF receptor antagonist, a TNF production inhibitor, a TNF receptor production inhibitor and a TNF releasing inhibitor.

27. A kit, comprising the combination of claim 10 and instructions for administration of the components for treatment of a hemorrhagic viral infection.

28. An article of manufacture, comprising: packaging material; a tetracycline compound or a tetracycline-like compound(s) in an amount effective for treating a hemorrhagic viral infection; and a label indicating that the tetracycline compound is for use in treating a hemorrhagic viral infection.

29. A method for producing a cytokine-receptor-enriched blood product, comprising: treating blood or a fraction thereof with a tetracycline or tetracycline-like compound; and harvesting the plasma, wherein the plasma is enriched for cytokine receptors compared to the blood prior to treatment.

30. The method of claim 29, wherein the receptors are soluble tumor necrosis factor (TNF) receptors and/or interleukin-1 (IL-1) receptors.

31. The method of claim 29, wherein the blood is contacted in vitro.

32. The method of claim 29, wherein the blood is contacted in vivo.

33. The method of claim 29, further comprising harvesting the globulin fraction.

34. A method for producing cytokine-receptor-enriched compositions, comprising: treating white blood cells in vitro with a tetracycline or

tetracycline-like compound, whereby receptor expression is induced; and collecting extracellular medium.

35. The method of claim 34, further comprising: fractionating the medium to collect fraction(s) that contain the receptors.

36. The method of claim 34, wherein the receptors comprise soluble tumor necrosis factor (TNF) receptors and/or interleukin-1 (IL-1) receptors.

37. The method of claim 34, further comprising isolating IL-1 and/or TNF receptors therefrom.

38. A soluble receptor-containing composition produced by the method of claim 29.

39. A soluble receptor-containing composition produced by the method of claim 34.

40. A method of treatment of a mammal having an acute inflammatory condition, disease or disorder, comprising administering the composition of claim 59.

41. The method of claim 40, wherein the acute inflammatory condition is selected from the group consisting of acute inflammatory conditions associated with viral hemorrhagic diseases, parasitic diseases, bacterial infections, sepsis, cachexia, autoimmune disorders, acute cardiovascular events, chronic myelogenous leukemia and transplanted bone marrow-induced graft-versus-host disease, septic shock, immune complex-induced colitis, cerebrospinal fluid inflammation, autoimmune disorders, multiple sclerosis; inflammatory responses associated with trauma; systemic inflammatory response syndrome (SIRS), adult respiratory distress syndrome (ARDS), acute liver failure, inflammatory bowel disease and Crohn's disease.

42. A method of treatment of a mammal having an acute inflammatory condition, disease or disorder, comprising administering the composition of claim 39.

43. The method of claim 42, wherein the acute inflammatory condition is selected from the group consisting of acute inflammatory conditions associated with viral hemorrhagic diseases, parasitic diseases, bacterial infections, sepsis, cachexia, autoimmune disorders, acute cardiovascular events, chronic myelogenous leukemia and transplanted bone marrow-induced graft-versus-host disease, septic shock, immune complex-induced colitis, cerebrospinal fluid inflammation, autoimmune disorders, multiple sclerosis; inflammatory responses associated with trauma; systemic inflammatory response syndrome (SIRS), adult respiratory distress syndrome (ARDS), acute liver failure, inflammatory bowel disease and Crohn's disease.

44. A method for treatment or prophylaxis of an inflammatory disease, comprising administering an effective amount of a tetracycline or tetracycline-like compound, whereby the disease is treated or prevented, and wherein the disease, condition or disorder is selected from the group consisting of multiple sclerosis, rheumatoid arthritis, and inflammatory responses associated with systemic inflammatory response syndrome (SIRS), adult respiratory distress syndrome (ARDS), acute liver failure, inflammatory bowel disease, polytrauma, burns, major surgery or Crohn's disease.

45. The method of claim 44, wherein the tetracycline compound is selected from the group consisting of chlortetracycline, demeclocycline, doxycycline, methacycline, minocycline, oxytetracycline and tetracycline.

=> d his

(FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1 3111 S DENGUE
L2 6 S L1 AND 45AZ5
L3 6 S L2 AND PDK-27

```
L4            14 S L1 AND S16803
L5             9 S L4 NOT L2
L6             1 S L5 AND PDK-50
L7            12 S L1 AND CH53489
L8             7 S L7 NOT (L3 OR L6)
L9             0 S L8 AND PDK-20
L10            9 S L1 AND 341750
L11            4 S L10 NOT (L3 OR L6)

=> s l1 and tetravalent
         11754 TETRAVALENT
L12         95 L1 AND TETRAVALENT

=> s l12 and tetravalent/clm
          3500 TETRAVALENT/CLM
L13          2 L12 AND TETRAVALENT/CLM

=> s l13 not (l3 or l5 or l8)
L14          1 L13 NOT (L3 OR L5 OR L8)

=> d l14,cbib,clm

L14  ANSWER 1 OF 1  USPATFULL on STN
2005:117278 Multivalent carriers of bi-specific antibodies.
    Hansen, Hans J., Picayune, MS, UNITED STATES
    McBride, William J., Boonton, NJ, UNITED STATES
    Qu, Zhengxing, Warren, NJ, UNITED STATES
    Immunomedics, Inc., Morris Plains, NJ, UNITED STATES (U.S. corporation)
    US 2005100543 A1 20050512
    APPLICATION: US 2004-882151  A1  20040701 (10)
    PRIORITY: US 2003-483832P  20030701 (60)
    DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
CLM    What is claimed is:
       1. A bi-specific antibody comprising the structure [IgG1]-[scFv]2;
       wherein said antibody comprises a pair of heavy chains and a pair of
       light chains,  wherein each heavy chain comprises an IgG1 heavy chain
       and an scFv, wherein said scFv is fused to the C-terminus of said IgG 1
       heavy chain, optionally via a linker peptide.

       2. The antibody according to claim 1, wherein the binding sites formed
       by said heavy chain and said light chain specifically binds to an
       epitope on a targeted tissue.

       3. The antibody according to claim 2, wherein each of said scFv moieties
       specifically binds to a carrier epitope.

       4. The antibody according to claim 1, wherein said IgG1 is a human,
       humanized, chimeric, or CDR-grafted antibody.

       5. The antibody according to claim 1, wherein each of said scFv
       molecules is human, humanized, or CDR-grafted.

       6. The antibody according to claim 5, wherein said antibody further
       comprises a bioactive moiety.

       7. The antibody according to claim 6, wherein said bioactive moiety is
       selected from the group consisting of a drug, a prodrug, an enzyme, a
       hormone, an immunomodulator, an oligonucleotide; a radionuclide, an
       image enhancing agent and a toxin.

       8. The antibody according to claim 1, wherein said antibody is selected
       from the group consisting of [hMN14-IgG1]-[734scFv]2 and
       [hMN14-IgG1(1253A)]-[734scFv]2.

       9. The antibody according to claim 1, wherein said antibody is selected
       from the group consisting of [hMN14-IgG1]-[679scFv]2 and
       [hMN14-IgG1(1253A)]-[679scFv]2.

       10. The antibody according to claim 1, wherein said antibody is selected
       from the group consisting of [hA20-IgG1]-[734scFv]2 and
       [hA20-IgG1(1253A)]-[734scFv]2.

       11. The antibody according to claim 1, wherein said antibody is selected
       from the group consisting of [hA20-IgG1]-[679scFv]2 and
```

[hA20-IgG1(1253A)]-[679scFv]$_2$.

12. The antibody according to claim 1, wherein said antibody is selected from the group consisting of [hLL2-IgG1]-[734scFv]$_2$ and [hLL2-IgG1(1253A)]-[734scFv]$_2$.

13. The antibody according to claim 1, wherein said antibody is selected from the group consisting of [hLL2-IgG1]-[679scFv]$_2$ and [hLL2-IgG1(1253A)]-[670scFv]$_2$.

14. A binding complex comprising a **tetravalent** binding molecule bound to a targetable construct, wherein said **tetravalent** binding molecule comprises two binding sites for a carrier epitope and two binding sites for a target epitope, and wherein said targetable construct comprises a molecular scaffold and at least two carrier epitopes.

15. The binding complex according to claim 14, wherein said targetable construct comprises at least two pairs of carrier epitopes and wherein at least two of said **tetravalent** binding molecules are bound to said targetable construct.

16. The binding complex according to claim 15, wherein said at least two pairs of carrier epitopes comprise a first pair and a second pair, wherein said first and second pair are different epitopes, and wherein a first **tetravalent** binding molecule is bound to said first pair of carrier epitopes and a second **tetravalent** binding molecule is bound to said second pair of carrier epitopes.

17. The binding complex according to claim 16, wherein said first and second pair of carrier epitopes are different epitopes.

18. The binding complex according to claim 17, wherein said first and second **tetravalent** binding molecules bind to the same target epitope.

19. The binding complex according to claim 14, wherein said targetable construct is selected from the group consisting of IMP 246, IMP 156, IMP 192 and IMP 222.

20. The binding complex according to claim 14, wherein said carrier epitope is a hapten.

21. The binding complex according to claim 14, wherein said carrier epitope is a chelator, wherein said chelator optionally is bound to a metal ion.

22. The binding complex according to claim 21, wherein said chelator is selected from the group consisting of DTPA, DOTA, benzyl DTPA, NOTA, and TETA.

23. The binding complex according to claim 14, wherein said **tetravalent** binding molecule is a bi-specific antibody comprising the structure [IgG$_1$]-[scFv]2; wherein said antibody comprises a pair of heavy chains and a pair of light chains, wherein each heavy chain comprises an IgG1 heavy chain and an scFv, wherein said scFv is fused to the C-terminus of said IgG1 heavy chain, optionally via a linker peptide.

24. The binding complex according to claim 14, wherein said molecular scaffold is a peptide or peptide derivative.

25. The binding complex according to claim 14, wherein said target epitope is an antigen associated with a disease.

26. The binding complex according to claim 25, wherein said disease is selected from the group consisting of hyperproliferative disease, pathogenic disease, cancer, cardiovascular disease, neurodegenerative disease, metabolic disease, and autoimmune disease

27. The binding complex according to claim 26, wherein said target epitope is a tumor associated antigen associated with a type of cancer selected from the group consisting of acute lymphoblastic leukemia, acute myelogenous leukemia, biliary cancer, breast cancer, cervical cancer, chronic lymphocytic leukemia, chronic myelogenous leukemia, colorectal cancer, endometrial cancer, esophageal, gastric, head and neck cancer, Hodgkin's lymphoma, lung cancer, medullary thyroid,

non-Hodgkin's lymphoma, ovarian cancer, pancreatic cancer, glioma, melanoma, liver cancer, prostate cancer, and urinary bladder cancer.

28. The binding complex according to claim 27, wherein said target epitope is a tumor associated antigen selected from the group consisting of A3, antigen specific for A33 antibody, BrE3, CD1, CD1a, CD3, CD5, CD15, CD19, CD20, CD21, CD22, CD23, CD25, CD30, CD45, CD74, CD79a, CD80, HLA-DR, NCA 95, NCA90, HCG and its subunits, CEA, CSAp, EGFR, EGP-1, EGP-2, Ep-CAM, Ba 733, HER2/neu, KC4, KS-1, KS1-4, Le-Y, MAGE, MUC1, MUC2, MUC3, MUC4, PAM-4, PSA, PSMA, RS5, S100, TAG-72, p53, tenascin, IL-6, insulin growth factor-1 (IGF-1), Tn antigen, Thomson-Friedenreich antigens, tumor necrosis antigens, VEGF, 17-1A, an angiogenesis marker, a cytokine, an immunomodulator, an oncogene marker, an oncogene product, and other tumor associated antigens.

29. A method of treating a disease in a subject, comprising administering to a subject suffering from said disease (i) a **tetravalent** binding molecule comprising two binding sites for a carrier epitope and two binding sites for a target epitope, wherein said target epitope is an epitope associated with said disease, (ii) optionally, a clearing agent, and (iii) a targetable construct comprising a molecular scaffold and at least two carrier epitopes.

30. The method according to claim 29, wherein said disease is selected from the group consisting of hyperproliferative disease, pathogenic disease, cancer, cardiovascular disease, neurodegenerative disease, metabolic disease, and autoimmune disease.

31. The method according to claim 29, wherein said targetable construct further comprises a bioactive moiety.

32. A method of diagnosing/detecting a disease in a subject, comprising administering to a subject suspected of suffering from said disease (i) a **tetravalent** binding molecule comprising two binding sites for a carrier epitope and two binding sites for a target epitope, (ii) optionally, a clearing agent, and (iii) a targetable construct comprising a molecular scaffold and at least two carrier epitopes, wherein said construct comprises a detectable label.

33. The method according to claim 32, wherein said target epitope is comprised within, displayed by or released from one or more cells, tissues, organs or systems of said subject.

34. A kit, comprising (i) a **tetravalent** binding molecule comprising two binding sites for a carrier epitope and two binding sites for a target epitope, (ii) optionally, a clearing agent, and (iii) a targetable construct comprising a molecular scaffold and at least two carrier epitopes.

35. A pharmaceutical composition comprising a bispecific antibody according to claim 1.

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=> d his

     (FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

     FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1          3111 S DENGUE
L2             6 S L1 AND 45AZ5
L3             6 S L2 AND PDK-27
L4            14 S L1 AND S16803
L5             9 S L4 NOT L2
L6             1 S L5 AND PDK-50
L7            12 S L1 AND CH53489
L8             7 S L7 NOT (L3 OR L6)
L9             0 S L8 AND PDK-20
L10            9 S L1 AND 341750
L11            4 S L10 NOT (L3 OR L6)
L12           95 S L1 AND TETRAVALENT
L13            2 S L12 AND TETRAVALENT/CLM
L14            1 S L13 NOT (L3 OR L5 OR L8)

=> file wpids
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COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    41.16      41.37

FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006
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MOST RECENT THOMSON SCIENTIFIC UPDATE:      200682        <200682/DW>
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http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf


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    PLEASE SEE
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<


=> s dengue
L15         551 DENGUE

=> s l15 and 45AZ5
              2 45AZ5
L16           2 L15 AND 45AZ5

=> d l16,bib,ab,1-2

L16  ANSWER 1 OF 2  WPIDS COPYRIGHT 2006       THE THOMSON CORP on STN
Full Text
AN   2000-638318 [61]   WPIDS
DNC  C2000-192015 [61]
TI   Immunogenic composition comprising attenuated dengue-1, -2, -3 or -4
     virus useful as vaccines for stimulating immune system of individual to
     induce protection against all 4 dengue virus serotypes
DC   B04; D16
IN   DUBOIS D R; ECKELS K; ECKELS K H; HOKE C H; INNIS B L; KANESA-THASAN N;
     KANESSA-THASAN N; NIRANJAN K; NIRANJAN K T; PUTNAK J R; WELLINGTON S;
     PRTNAK J R
PA   (REED-N) REED ARMY INST RES WALTER; (USSA-C) US SEC OF ARMY
CYC  81
PIA  WO 2000057907   A2 20001005 (200061)* EN  95[8]
     AU 2000040382   A  20001016 (200106)  EN
     EP 1165127      A2 20020102 (200209)  EN
     KR 2002008136   A  20020129 (200253)  KO
     CN 1351502      A  20020529 (200258)  ZH
     JP 2002540168   W  20021126 (200307)  JA  92
     US 6638514      B1 20031028 (200372)  EN
     BR 2000010969   A  20031223 (200406)  PT
     MX 2001009683   A1 20030601 (200417)  ES
     AU 779280       B2 20050113 (200512)  EN
     MX 230950       B  20050930 (200617)  ES
     CN 1191092      C  20050302 (200634)  ZH
ADT  WO 2000057907 A2 WO 2000-US8199 20000324; US 6638514 B1 Provisional US
     1999-126313P 19990326; US 6638514 B1 Provisional US 2000-181724P 20000211;
     AU 2000040382 A AU 2000-40382 20000324; AU 779280 B2 AU 2000-40382
     20000324; BR 2000010969 A BR 2000-10969 20000324; CN 1351502 A CN
     2000-807995 20000324; EP 1165127 A2 EP 2000-919748 20000324; JP 2002540168
     W JP 2000-607657 20000324; US 6638514 B1 US 2000-535117 20000324; EP
     1165127 A2 WO 2000-US8199 20000324; JP 2002540168 W WO 2000-US8199
     20000324; BR 2000010969 A WO 2000-US8199 20000324; MX 2001009683 A1 WO
     2000-US8199 20000324; MX 230950 B WO 2000-US8199 20000324; KR 2002008136 A
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KR 2001-712302 20010926; MX 2001009683 A1 MX 2001-9683 20010926; MX 230950 B MX 2001-9683 20010926; CN 1191092 C CN 2000-807995 20000324

FDT AU 779280 B2 Previous Publ AU 2000040382 A; AU 2000040382 A Based on WO 2000057907 A; EP 1165127 A2 Based on WO 2000057907 A; JP 2002540168 W Based on WO 2000057907 A; BR 2000010969 A Based on WO 2000057907 A; MX 2001009683 A1 Based on WO 2000057907 A; AU 779280 B2 Based on WO 2000057907 A; MX 230950 B Based on WO 2000057907 A

PRAI US 2000-181724P 20000211
US 1999-126313P 19990326
US 2000-535117 20000324

AB WO 2000057907 A2 UPAB: 20060117
NOVELTY - An immunogenic composition (I) comprising more than one attenuated **dengue** virus (DV) such as **dengue**-1, -2, -3 or -4, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a multivalent live attenuated DV vaccine (II) comprising any combination of DV serotypes such as such as **dengue**-1, -2, -3 or -4.

MECHANISM OF ACTION - Vaccine. The **dengue** 2 strain S16803 virus produced from the 50th passage in PDK cells was tested in three volunteers. No recipients of the PDK 50 vaccine developed viremia, yet two of 3 developed low-titer neutralizing antibody by day 60. These findings suggested that the vaccine virus was diminished in infectivity for humans. By contrast, two of 3 **dengue**-2 PDK (primary dog kidney) 40 vaccinees had demonstrable viremia, and all developed high titer antibody after vaccination. Infectivity of the **dengue**-2 PDK 30 vaccine was highest:viremia was detected in all 10 volunteers and all subjects seroconverted with neutralizing antibody titers of greater than 1:60 by day 60.

USE - (I) is useful for stimulating DV-specific immune response (claimed).

ADVANTAGE - The vaccine confers protection against all four serotypes of **dengue**.

L16 ANSWER 2 OF 2 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2000-602361 [57] WPIDS
DNC C2000-180351 [57]
TI Replicating **dengue** virus strains to high titer growth in mammalian cells for use as a vaccine
DC B04; D16
IN ECKELS K H; INNIS B L; PUTNAK J R
PA (REED-N) REED ARMY INST RES WALTER; (USSA-C) US SEC OF ARMY
CYC 81
PIA WO 2000058444 A2 20001005 (200057)* EN 49[2]
AU 2000040403 A 20001016 (200106) EN
EP 1165756 A2 20020102 (200209) EN
JP 2002539821 W 20021126 (200307) JA 46
US 6613556 B1 20030902 (200359) EN
AU 776638 B2 20040916 (200479) EN

ADT WO 2000058444 A2 WO 2000-US8276 20000324; US 6613556 B1 Provisional US 1999-126316P 19990326; US 6613556 B1 Provisional US 2000-182065P 20000211; AU 2000040403 A AU 2000-40403 20000324; AU 776638 B2 AU 2000-40403 20000324; EP 1165756 A2 EP 2000-919774 20000324; JP 2002539821 W JP 2000-608725 20000324; US 6613556 B1 US 2000-534724 20000324; EP 1165756 A2 WO 2000-US8276 20000324; JP 2002539821 W WO 2000-US8276 20000324

FDT AU 776638 B2 Previous Publ AU 2000040403 A; AU 2000040403 A Based on WO 2000058444 A; EP 1165756 A2 Based on WO 2000058444 A; JP 2002539821 W Based on WO 2000058444 A; AU 776638 B2 Based on WO 2000058444 A

PRAI US 2000-182065P 20000211
US 1999-126316P 19990326
US 2000-534724 20000324

AB WO 2000058444 A2 UPAB: 20050411
NOVELTY - Replicating **dengue** virus to high titer growth comprises infecting cells from a continuous cell line that lacks adventitious agents to the extent that the cells are suitable to be certified for mammalian virus vaccine production with the high titer growth strain, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a live attenuated **dengue** virus vaccine comprising any combination of **dengue** virus serotypes selected from **dengue** 1, **dengue** 2, **dengue** 3 and **dengue** 4 produced by the above method.

ACTIVITY - Virucide.

MECHANISM OF ACTION - Vaccine.

Dengue 2 strain S16803 virus produced from the 50th passage in primary dog kidney (PDK) cells was tested in 3 volunteers. No oral temperatures more than 38 degreesC were recorded but 2 of the volunteers had transient mild symptoms of malaise, headache and eye symptoms.

Laboratory findings included mild ALT elevations (less than 2x normal) in 2 of 3 and mild leukopenia in 1 of 3 volunteers. The PDK 30 vaccine tested in 10 subjects was under attenuated and produced symptoms compatible with mild to moderate **dengue**. Four volunteers developed low grade fever over days 9-14 post vaccination. Eighty percent developed rash and the majority experienced eye symptoms, headaches and malaise.

USE - The virus produced by the method is used in an immunogenic composition or as a live attenuated **dengue** virus vaccine (both claimed) to provide a prophylactic or therapeutic response to a **dengue** virus infection.

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=> d his

     (FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

     FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1          3111 S DENGUE
L2             6 S L1 AND 45AZ5
L3             6 S L2 AND PDK-27
L4            14 S L1 AND S16803
L5             9 S L4 NOT L2
L6             1 S L5 AND PDK-50
L7            12 S L1 AND CH53489
L8             7 S L7 NOT (L3 OR L6)
L9             0 S L8 AND PDK-20
L10            9 S L1 AND 341750
L11            4 S L10 NOT (L3 OR L6)
L12           95 S L1 AND TETRAVALENT
L13            2 S L12 AND TETRAVALENT/CLM
L14            1 S L13 NOT (L3 OR L5 OR L8)

     FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006
L15          551 S DENGUE
L16            2 S L15 AND 45AZ5

=> s l15 and S16803
               2 S16803
L17            2 L15 AND S16803

=> s l17 not l16
L18            0 L17 NOT L16

=> s l15 and CH53489
               1 CH53489
L19            1 L15 AND CH53489

=> s l19 not l16
L20            1 L19 NOT L16

=> d l20,bib,ab

L20  ANSWER 1 OF 1  WPIDS COPYRIGHT 2006       THE THOMSON CORP on STN
Full Text
AN   1999-034671 [03]   WPIDS
DNC  C1999-010426 [03]
TI   Detection of dengue virus infection  - comprises use of reverse
     transcriptase-polymerase chain reaction as a rapid assay for all
     serological types
DC   B04; D16
IN   ENNIS F A; ISHIKO H; SUDIRO T M
PA   (UYMA-N) UNIV MASSACHUSETTS
CYC  23
PIA  WO 9849351      A1 19981105 (199903)* EN  27[2]
     AU 9872621      A  19981124 (199914)  EN
     US 5939254      A  19990817 (199939)  EN
ADT  WO 9849351 A1 WO 1998-US8526 19980428; US 5939254 A US 1997-840344
     19970428; AU 9872621 A AU 1998-72621 19980428
FDT  AU 9872621 A Based on WO 9849351 A
PRAI US 1997-840344 19970428
AB   WO 1998049351 A1   UPAB: 20060114
     The following are claimed: (1) a method of detecting dengue virus in a
     biological sample comprises: (a) incubating RNA extracted from the sample
     with reverse transcriptase and a first dengue virus specific primer (P1)
     under conditions sufficient for double stranded nucleic acid formation;
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(b) adding a second **dengue** virus specific primer (P2) and a thermostable DNA polymerase; (c) incubating under conditions sufficient to allow the double stranded nucleic acid, if present, to be PCR amplified and form reaction products, and (d) detecting the reaction products as an indication of **dengue** virus in the sample where P1 comprises 15-28 nucleotides, including at least 15 nucleotides of the sequence 5'-TCTCTCCCAGCGTCAATA-3' (I) and is fully complementary to a region in the **dengue** viral nucleic acid complementary to sequence (I), and P2 comprises 15-28 nucleotides, including at least 15 nucleotides of the sequence 5'-AAACCGTGCTGCCTGTAG-3' (II) and is fully complementary to a region in the **dengue** viral nucleic acid complementary to sequence (II). Alternatively, in step (b), the second primer is identical to a region in the **dengue** viral nucleic acid that includes sequence (II), and a third primer (P3) being 15-28 nucleotides, including at least 15 consecutive nucleotides of the sequence 5'-AAACTGTGCAGCCTGTAG-3' (III) is added; (2) a kit comprising P1, P2 and optionally P3, and reagents for performing RT-PCR; (3) a method of quantitating **dengue** virus in a biological sample, comprising: (a) mixing RNA extracted from the sample with a known quantity of competitor RNA; (b) incubating the mixture with P1 under conditions sufficient for double stranded nucleic acid formation; (c) adding a second **dengue** virus-specific primer (P4) and a thermostable DNA polymerase; (d) incubating under conditions sufficient to allow the double stranded nucleic acid to be PCR amplified and form reaction products; (e) detecting the reaction products, and (f) comparing the amount of reaction product obtained with the amount obtained in the absence of competitor RNA, or quantitating the reaction products obtained by comparison to known amounts of competitor RNA where P4 comprises 15-28 nucleotides, including at least 15 nucleotides of the sequence 5'-AAACCGTGCAGCCTGTAG-3' (IV) and is fully complementary to a region in the **dengue** viral nucleic acid complementary to sequence (IV); (4) a method of determining the serotype of **dengue** virus in a biological sample, comprising: (a) as in (1), but using labelled nucleotides in the PCR to form labelled reaction products; (b) adding aliquots of reaction products to separate microwells, each of which is coated with a probe specific for one of the four **dengue** virus serotypes, and (c) detecting hybridisation; (5) P1, P2, P3 and P4, and (6) sequences (I)-(IV).

USE - The diagnostic test is particularly useful to clinically identify children with **dengue** virus, allowing early management of patients with the infection (disclosed).

ADVANTAGE - The methods provide a means to test for all four **dengue** virus serotypes in a shorter time than prior art methods.

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     (FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

     FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
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L2             6 S L1 AND 45AZ5
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L8             7 S L7 NOT (L3 OR L6)
L9             0 S L8 AND PDK-20
L10            9 S L1 AND 341750
L11            4 S L10 NOT (L3 OR L6)
L12           95 S L1 AND TETRAVALENT
L13            2 S L12 AND TETRAVALENT/CLM
L14            1 S L13 NOT (L3 OR L5 OR L8)

     FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006
L15          551 S DENGUE
L16            2 S L15 AND 45AZ5
L17            2 S L15 AND S16803
L18            0 S L17 NOT L16
L19            1 S L15 AND CH53489
L20            1 S L19 NOT L16

=> s l15 and 341750
               4 341750
L21            4 L15 AND 341750
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=> s l21 not (l16 or l17 or l19)
L22          2 L21 NOT (L16 OR L17 OR L19)

=> d l22,bib,ab,1-2

L22  ANSWER 1 OF 2  WPIDS COPYRIGHT 2006       THE THOMSON CORP on STN
Full Text
AN   2000-647205 [62]   WPIDS
DNC  C2000-195764 [62]
TI   Immunogenic composition comprising attenuated dengue-4 virus useful as
     vaccines for stimulating immune system of individual to induce protection
     against dengue-4 virus serotype
DC   B04; D16
IN   DUBOIS D R; ECKELS K H; HOKE C H; INNIS B L; PUTNAK J R; VAUGHN D; VAUGHN
     D W
PA   (REED-N) REED ARMY INST RES WALTER; (USSA-C) US SEC OF ARMY
CYC  81
PIA  WO 2000057910   A1 20001005 (200062)* EN  101[8]
     AU 2000040404   A  20001016 (200106)  EN
     EP 1165129      A1 20020102 (200209)  EN
     JP 2002540171   W  20021126 (200307)  JA  95
     US 6537557      B1 20030325 (200325)  EN
ADT  WO 2000057910 A1 WO 2000-US8277 20000324; US 6537557 B1 Provisional US
     1999-126318P 19990326; US 6537557 B1 Provisional US 2000-182068P 20000211;
     AU 2000040404 A AU 2000-40404 20000324; EP 1165129 A1 EP 2000-919775
     20000324; JP 2002540171 W JP 2000-607660 20000324; US 6537557 B1 US
     2000-534726 20000324; EP 1165129 A1 WO 2000-US8277 20000324; JP 2002540171
     W WO 2000-US8277 20000324
FDT  AU 2000040404 A Based on WO 2000057910 A; EP 1165129 A1 Based on WO
     2000057910 A; JP 2002540171 W Based on WO 2000057910 A
PRAI US 2000-182068P 20000211
     US 1999-126318P 19990326
     US 2000-534726 20000324
AB   WO 2000057910 A1   UPAB: 20050412
      NOVELTY - An immunogenic composition (I) comprising an attenuated
     dengue-4 virus, is new.
          DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the
     following:
          (1) a DNA molecule encoding a attenuated dengue-4 virus genome
     comprising the nucleotide sequence of dengue-4 virus with American type
     culture collection (ATCC) accession number VR-2652; and
          (2) attenuating dengue-4 virus, comprising passaging the virus in
     dog kidney cells and testing the ability of virus to cause disease in a
     mammal after each passage, in which the virus is attenuated when it is
     unable to cause disease in the mammal.
          ACTIVITY - Antiviral.
          MECHANISM OF ACTION - Vaccine. Eight volunteers received 10 to the
     power 5 plaque forming units (pfu) of the PDK 20 Dengue 4 341750
     vaccine and viremia and antibody response developed in five (63 %). The
     vaccine prepared from a lower passage of this candidate. Virus was
     isolated from a single volunteer, on days 8 and 10 following vaccination,
     with maximum titer of 15 pfu/ml. The volunteer subsequently developed a
     neutralizing antibody titer of 450 with a secondary hemagglutination
     inhibition (HAI) response, and was found to have been previously exposed
     to St. Louis encephalitis virus (PRNT titer 1:20 before vaccination). The
     two volunteers without detectable viremia developed neutralizing titers of
     1:10 and 1:40 by day 30 after vaccination.
          USE - (I) is useful for stimulating dengue-4 specific immune
     response (claimed).

L22  ANSWER 2 OF 2  WPIDS COPYRIGHT 2006       THE THOMSON CORP on STN
Full Text
AN   2000-611687 [58]   WPIDS
DNC  C2000-183093 [58]
TI   Immunogenic composition containing attenuated dengue-1 virus, useful as
     a protective vaccine, inducing humoral and cellular responses
DC   B04; D16
IN   DUBOIS D R; ECKELS K H; HOKE C H; INNIS B L; PUTNAK J R; VAUGHN D W
PA   (REED-N) REED ARMY INST RES WALTER
CYC  81
PIA  WO 2000057908   A2 20001005 (200058)* EN  96[8]
     AU 2000041792   A  20001016 (200106)  EN
     EP 1165131      A2 20020102 (200209)  EN
     JP 2002540169   W  20021126 (200307)  JA  94
ADT  WO 2000057908 A2 WO 2000-US8201 20000324; AU 2000041792 A AU 2000-41792
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20000324; EP 1165131 A2 EP 2000-921482 20000324; JP 2002540169 W JP 2000-607658 20000324; EP 1165131 A2 WO 2000-US8201 20000324; JP 2002540169 W WO 2000-US8201 20000324

FDT AU 2000041792 A Based on WO 2000057908 A; EP 1165131 A2 Based on WO 2000057908 A; JP 2002540169 W Based on WO 2000057908 A

PRAI US 2000-182064P 20000211
US 1999-126317P 19990326

AB WO 2000057908 A2 UPAB: 20050411

NOVELTY - An immunogenic composition (A) containing at least 1 attenuated **dengue**-1 virus (I) in a vehicle, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(a) a method for stimulating a **dengue**-1 virus specific response by administration of (A);

(b) a DNA molecule comprising the genome of (I) deposited as ATCC VR-2648; and

(c) a method for attenuating **dengue**-1 virus by passaging in dog kidney cells and testing for the ability to cause disease in animals after each passage.

ACTIVITY - Antiviral.

MECHANISM OF ACTION - Vaccine; stimulation of a specific immune response, both antibody and cellular (principally of Th1 type).

The immune response is mainly specific to the **dengue**-1 serotype but with some response to other serotypes. When 12 subjects were inoculated with the preferred attenuated virus ATCC VR-2648, all became seropositive for neutralizing antibodies after a single treatment.

USE - (A) are useful in vaccines to induce a protective (I)-specific immune response against **Dengue** viruses.

ADVANTAGE - (I) remain infectious in humans but do not cause disease.

=> d his

(FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006

L1	3111	S	DENGUE
L2	6	S	L1 AND 45AZ5
L3	6	S	L2 AND PDK-27
L4	14	S	L1 AND S16803
L5	9	S	L4 NOT L2
L6	1	S	L5 AND PDK-50
L7	12	S	L1 AND CH53489
L8	7	S	L7 NOT (L3 OR L6)
L9	0	S	L8 AND PDK-20
L10	9	S	L1 AND 341750
L11	4	S	L10 NOT (L3 OR L6)
L12	95	S	L1 AND TETRAVALENT
L13	2	S	L12 AND TETRAVALENT/CLM
L14	1	S	L13 NOT (L3 OR L5 OR L8)

FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006

L15	551	S	DENGUE
L16	2	S	L15 AND 45AZ5
L17	2	S	L15 AND S16803
L18	0	S	L17 NOT L16
L19	1	S	L15 AND CH53489
L20	1	S	L19 NOT L16
L21	4	S	L15 AND 341750
L22	2	S	L21 NOT (L16 OR L17 OR L19)

=> s l15 and tetravalent

	6792		TETRAVALENT
L23	6		L15 AND TETRAVALENT

=> s l23 not (l16 or l17 or l19)

L24	6		L23 NOT (L16 OR L17 OR L19)

=> d l24,bib,ab,1-6

L24 ANSWER 1 OF 6 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN

Full Text

AN 2004-553366 [53] WPIDS

DNC C2004-202523 [53]

TI Novel chemically modified short interfering nucleic acid molecule downregulating expression of target gene by RNA interference, useful for inhibiting target gene associated with inflammation, autoimmune disease, cancer

DC C03; C06; D16

IN RADHAKRISHNAN P

PA (ICHE-N) ICHEM TECHNOLOGIES; (RADH-I) RADHAKRISHNAN P

CYC 105

PIA WO 2004061081 A2 20040722 (200453)* EN 61[5]
AU 2003299864 A1 20040729 (200477) EN
AU 2003299864 A8 20051110 (200634) EN

ADT WO 2004061081 A2 WO 2003-US41126 20031223; AU 2003299864 A1 AU 2003-299864 20031223; AU 2003299864 A8 AU 2003-299864 20031223

FDT AU 2003299864 A1 Based on WO 2004061081 A; AU 2003299864 A8 Based on WO 2004061081 A

PRAI US 2002-436599P 20021227

AB WO 2004061081 A2 UPAB: 20060122

NOVELTY - A chemically modified short interfering nucleic acid molecule (I) downregulating expression of target gene by RNA interference, where molecule comprises non-nucleotidic trivalent linker having three terminal ends, where first and second oligonucleotide that is complementary to or homologous with target gene, is attached to first and second terminal end, respectively, and hydrophobic moiety is attached to third terminal end, is new.

DETAILED DESCRIPTION - A chemically modified short interfering nucleic acid molecule (siRNA) (I) capable of downregulating the expression of a target gene by RNA interference, where the molecule comprises a non-nucleotidic trivalent linker having three terminal ends, where a first oligonucleotide is attached to a first terminal end and a second oligonucleotide is attached to a second terminal end and a hydrophobic moiety is attached to a third terminal end and where at least one of the first and second oligonucleotides, is complementary to or homologous with, the target gene, the molecule comprises a single-stranded hairpin structure having a loop region and self-complementary sense and antisense oligonucleotide regions, where the antisense region is complementary to a portion of the target gene and where the loop region comprises a non-nucleotide trivalent linker substituted with a hydrophobic moiety, or the molecule comprises a trivalent linker having three terminal ends, where a first oligonucleotide is attached to a first terminal end and a second oligonucleotide is attached to a second terminal end and a solid support is attached to a third terminal end and where at least one of the first and second oligonucleotides, is complementary to or homologous with, the target gene, and has structural formula 1, 2, 3 and 4.

G = oligonucleotide;

L = trivalent linker; and

Z1 = hydrophobic moiety.

Where G is complementary to or homologous with a target gene.

R1 = antisense or sense oligonucleotide complementary to R3; and

R3 = a sense or antisense oligonucleotide complementary to R1.

R1 = sense or antisense oligonucleotide that is complementary to R3;

R3 = a sense or antisense oligonucleotide that is complementary to R1;

A and R7 = S or O;

R8 = OH, SH or NR4R5;

R4, R5 and R6 = H, alkyl, substituted alkyl, alkaryl or substituted alkaryl, aralkyl or substituted aralkyl;

X = S, O or NR4;

Y = (CH2)n;

m = 0-20;

n = 1-20;

D = a long-chain aliphatic linker which is optionally interrupted by one or more heteroatoms; and

V = ester moiety or an amide moiety.

Q = hexavalent atom such as sulfur, pentavalent atom such as phosphorus, **tetravalent** atom such as sulfur, or carbon in which case the bond between Q and R11 does not exist;

R10 = O, S or NH except that when Q = S, R10 and R11 = O; and

R12 = O, S or NH.

Where R1 and R3 is an antisense oligonucleotide, R1 and R3 are also complementary to the target gene.

An INDEPENDENT CLAIM is also included for a pharmaceutical composition (PC) comprising (I) and an excipient, where the hairpin siRNA molecules with loop region comprises a non-nucleotidic trivalent linker or spacer substituted with the hydrophobic chemical moiety.

ACTIVITY - Antiinflammatory; Immunosuppressive; CNS-Gen.; Cytostatic; Antimicrobial; Virucide; Hepatotropic.

No biological data is given.

MECHANISM OF ACTION - Downregulates the expression of a target gene (claimed).

USE - (I) is useful for inhibiting the expression of a target gene which involves contacting cell comprising the target gene with (I) that mediates the inhibition of the expression of target gene, where the hairpin siRNA molecules having the loop region comprises a non-nucleotidic trivalent linker or spacer substituted with the hydrophobic chemical moiety. The target gene is a viral gene associated with replication and/or pathogenesis of virus. PC is useful for inhibiting the target gene associated with onset or maintenance of disease such as inflammation, autoimmune disease, CNS disease and disorders, cancer, infectious diseases and metabolic disorders (all claimed). (I) is useful for treating viral infection such as hepatitis C virus, yellow fever virus, **Dengue** virus, etc.

DESCRIPTION OF DRAWINGS - The figure shows mechanism of RNA interference.

L24 ANSWER 2 OF 6 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2004-053338 [05] WPIDS
DNC C2004-021491 [05]
TI Vaccine composition comprising a chimeric flavivirus comprising the capsid and non-structural proteins of yellow fever virus, and pre-membrane and envelop proteins of **Dengue**-1, 2, 3 and 4 virus, for treating or preventing **dengue** infection
DC B04; D16
IN GUIRAKHOO F
PA (ACAM-N) ACAMBIS INC; (GUIR-I) GUIRAKHOO F
CYC 101
PIA WO 2003101397 A2 20031211 (200405)* EN 96[9]
AU 2003239932 A1 20031219 (200449) EN
US 20040259224 A1 20041223 (200504) EN
AU 2003239932 A8 20051103 (200629) EN
ADT WO 2003101397 A2 WO 2003-US17359 20030602; US 20040259224 A1 Provisional US 2002-385013P 20020531; AU 2003239932 A1 AU 2003-239932 20030602; US 20040259224 A1 US 2003-452610 20030602; AU 2003239932 A8 AU 2003-239932 20030602
FDT AU 2003239932 A1 Based on WO 2003101397 A; AU 2003239932 A8 Based on WO 2003101397 A
PRAI US 2002-385013P 20020531
US 2003-452610 20030602
AB WO 2003101397 A2 UPAB: 20050527
NOVELTY - Vaccine composition for inducing an immune response to four serotypes of **dengue** virus in a patient, comprising a chimeric flavivirus comprising the capsid and non-structural proteins of yellow fever virus (YFV), and the pre-membrane and envelop proteins of **Dengue**-1, **Dengue**-2, **Dengue**-3 and **Dengue**-4 virus.

ACTIVITY - Immunostimulant; Virucide. No biological data given.

MECHANISM OF ACTION - Vaccine.

USE - The composition is useful as a vaccine for treating or preventing **dengue** infection.

L24 ANSWER 3 OF 6 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2004-022612 [02] WPIDS
DNC C2004-007053 [02]
TI New **tetravalent** vaccine containing a common nucleotide deletion in the 3' untranslated region of **dengue** types 1, 2, 3, and 4, useful for preventing of disease in humans caused by **dengue** virus, or for inducing immune response
DC B04; D16
IN BLANEY J; FALGOUT B; HANLEY K; MARKOFF L; MURPHY B R; WHITEHEAD S S
PA (USSH-C) US DEPT HEALTH & HUMAN SERVICES
CYC 102
PIA WO 2003092592 A2 20031113 (200402)* EN 181[12]
AU 2003231185 A1 20031117 (200442) EN
EP 1554301 A2 20050720 (200547) EN
JP 2005532044 W 20051027 (200571) JA 186
ADT WO 2003092592 A2 WO 2003-US13279 20030425; AU 2003231185 A1 AU 2003-231185 20030425; EP 1554301 A2 EP 2003-724319 20030425; EP 1554301 A2 WO 2003-US13279 20030425; JP 2005532044 W WO 2003-US13279 20030425; JP 2005532044 W JP 2004-500777 20030425

FDT AU 2003231185 A1 Based on WO 2003092592 A; EP 1554301 A2 Based on WO 2003092592 A; JP 2005532044 W Based on WO 2003092592 A
PRAI US 2002-436500P 20021223
US 2002-377860P 20020503
AB WO 2003092592 A2 UPAB: 20060120
NOVELTY - An immunogenic composition being **tetravalent** and containing a common nucleotide deletion in the 3' untranslated region of **dengue** types 1, 2, 3, and 4.

DETAILED DESCRIPTION - The composition comprises a nucleic acid comprising a first nucleotide sequence encoding at least one structural protein from a first **dengue** virus, and a second nucleotide sequence encoding non-structural proteins from a second **dengue** virus attenuated by a deletion of about 30 nucleotides from the 3' untranslated region of the **dengue** genome corresponding to the TL2 stem-loop structure.

INDEPENDENT CLAIMS are also included for the following:

(1) a method of reducing an immune response in a subject by administering a composition;

(2) a method of preventing disease caused by **dengue** virus in a subject by administering a vaccine defined above;

(3) an isolated nucleic acid probe or primer that selectively hybridizes with and possesses at least 5 nucleotides complementary to the nucleic acid or the complementary strand of the nucleic acid encoding the cleavage site that separates the capsid protein and the premembrane protein of the nucleic acid chimera comprising the composition above; and

(4) a composition, optionally comprising a mutation selected from temperature sensitivity in Fete cells or the human liver cell line HUH-7, host-cell restriction in mosquito cells or the human liver cell line HUH-7, host-cell adaptation for improved replication in Fete cells, or attenuation in mice or monkeys, and comprising a member selected from 256 sets of **tetravalent** vaccine.

ACTIVITY - Virucide; Immunostimulant.

MECHANISM OF ACTION - Vaccine. ~~**Dengue** virus-seronegative monkeys~~ were injected subcutaneously with 5.0 log10 PFU of virus in a 1 ml dose divided between 2 injections in each side of the upper shoulder area. Monkeys were observed daily and blood was collected on days 0-10 and 28, and serum was stored at -70degreesC. Virus titer in serum samples was determined by plaque assay in Vero cells. Plaque reduction neutralization titers were determined for the day 28 serum samples. Monkeys were challenged on day 28 with a single dose of 5.0 log10 PFU of wild type rDEN1 and blood was collected for 10 days. Monkeys inoculated with full length wild type rDEN1 were viremic for 2-3 days, and monkeys inoculated with rDEN1DELTA30 were viremic for les than 1 day indicating that the DELTA30 mutation is capable of attenuating DEN1. Immune response was lower following inoculation with rDEN1DELTA30 compared to the wild type rDEN1, yet sufficiently high to protect the animals against wild type DEN1 virus challenge. Wild type rDEN1 virus was not detected in any serum sample collected following virus challenge, indicating that monkeys were completely protected following immunization with either full length wild type rDEN1 or recombinant virus rDEN1DELTA30.

USE - The composition is useful for inducing an immune response. The **tetravalent** vaccine is useful in the prevention of disease in humans caused by **dengue** virus (all claimed).

ADVANTAGE - Unlike previous **tetravalent** vaccine, the new **tetravalent** vaccine is unique since they contain a common shared attenuating mutation which eliminates the possibility of generating a virulent wild type virus in a subject to be vaccinated since each component of the vaccine possesses the same DELTA30 attenuating deletion mutation. The vaccine also is able to induce humoral and cellular responses against al of the (non-)structural proteins present in each **dengue** virus serotype.

L24 ANSWER 4 OF 6 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2003-120809 [11] WPIDS
DNC C2003-031374 [11]
DNN N2003-096140 [11]
TI New mutated flavivirus, useful for fine tuning the attenuation and growth characteristics of **dengue** virus vaccines for the prevention and/or treatment of **dengue** virus infection
DC B04; D16; S03
IN BLANEY J E; HANLEY K A; MURPHY B R; WHITEHEAD S S
PA (BLAN-I) BLANEY J E; (HANL-I) HANLEY K A; (MURP-I) MURPHY B R; (USSH-C) US DEPT HEALTH & HUMAN SERVICES; (WHIT-I) WHITEHEAD S S
CYC 99
PIA WO 2002095075 A1 20021128 (200311)* EN 246[12]

BR 2002009943 A 20040330 (200424) PT
EP 1402075 A1 20040331 (200424) EN
AU 2002312011 A1 20021203 (200452) EN
US 20050010043 A1 20050113 (200506) EN
IN 2003002184 P1 20050603 (200602) EN

ADT WO 2002095075 A1 WO 2002-US16308 20020522; US 20050010043 A1 Provisional US 2001-293049P 20010522; AU 2002312011 A1 AU 2002-312011 20020522; BR 2002009943 A BR 2002-9943 20020522; EP 1402075 A1 EP 2002-739358 20020522; BR 2002009943 A WO 2002-US16308 20020522; EP 1402075 A1 WO 2002-US16308 20020522; US 20050010043 A1 Cont of WO 2002-US16308 20020522; IN 2003002184 P1 WO 2002-US16308 20020522; US 20050010043 A1 US 2003-719547 20031121; IN 2003002184 P1 IN 2003-DN2184 20031215

FDT BR 2002009943 A Based on WO 2002095075 A; EP 1402075 A1 Based on WO 2002095075 A; AU 2002312011 A1 Based on WO 2002095075 A

PRAI US 2001-293049P 20010522
WO 2002-US16308 20020522
US 2003-719547 20031121

AB WO 2002095075 A1 UPAB: 20060202

NOVELTY - A flavivirus (I) comprises a phenotype in which the viral genome is modified by introduction of a mutation, singly or in combination, taken from mutations from recombinant virus bearing Vero adaptation mutations, putative Vero cell adaptation mutations of **dengue** type 4 virus or mutations known to attenuate **dengue** type 4 virus, is new.

DETAILED DESCRIPTION - A flavivirus (I) comprises a phenotype in which the viral genome is modified by introduction of a mutation, singly or in combination, taken from mutations from recombinant virus bearing Vero adaptation mutations, putative Vero cell adaptation mutations of **dengue** type 4 virus or mutations known to attenuate **dengue** type 4 virus, together with their corresponding wild type amino acid residue in other **dengue** virus, given in the specification.

INDEPENDENT CLAIMS are also included for the following:

(1) a pharmaceutical composition comprising a vehicle and (I);

(2) a kit comprising a pharmaceutical composition of (1) in a pack or dispenser device and instructions for administration;

(3) a method of producing neutralizing antibodies against **dengue** virus, comprising administering a pharmaceutical composition of (1);

(4) a **tetravalent** vaccine comprising a vehicle and (I);

(5) a live attenuated vaccine comprising a vehicle and (I);

(6) an inactivated vaccine comprising a vehicle and (I);

(7) a cDNA or RNA molecule encoding (I);

(8) a method of preparing a flavivirus, comprising synthesizing full length viral genomic RNA in vitro using cDNA molecule that encodes (I), transfecting cultured cells with the viral genomic RNA to produce virus, and isolating the virus from the cultured cells;

(9) a method of making a pharmaceutical composition, comprising combining a vehicle and (I);

(10) a method of identifying a mutation that restricts replication in human liver cells, comprising introducing mutations into a **dengue** virus genome to make mutant viruses, screening the mutant viruses for a phenotype characterized by host-cell adaptation for improved replication in Vero cells, and determining the genetic basis for the phenotype by direct sequence analysis of the virus genome;

(11) a method of identifying a mutation that promotes growth in Vero cells, comprising introducing mutations into a **dengue** virus genome to make mutant viruses, screening the mutant viruses for a phenotype characterized by host-cell restriction in human liver cells, and determining the genetic basis for the phenotype by direct sequence analysis of the virus genome; and

(12) a method of assembling a menu of mutations for use in fine-tuning the attenuation and growth characteristics of recombinant **dengue** viruses, comprising introducing mutations into a **dengue** virus genome to make mutant viruses, screening the mutant viruses for a phenotype characterized by temperature sensitivity in Vero cells or human liver cells, host cell restriction in mosquito cells or human liver cells, host cell adaptation for improved replication in Vero cells, or attenuation in mice, determining the genetic basis for the phenotype by direct sequence analysis of the virus genome, and performing multiple iterations on the preceding steps, where a menu of mutations is assembled.

ACTIVITY - Virucide.

MECHANISM OF ACTION - Vaccine.

A DEN-4 mutant bearing a 30 nucleotide deletion introduced into its 3' untranslated region by site-directed mutagenesis was evaluated for the attenuation in humans and rhesus monkeys. The results showed that each of the 20 vaccines developed a significant rise in serum neutralizing antibody titer against DEN-4 by day 28. The level of serum neutralizing

antibody was similar in viremic and non-viremic vaccines.

USE - The methods and compositions of the present invention are useful for fine tuning the attenuation and growth characteristics of **dengue** virus vaccines for the prevention and/or treatment of **dengue** virus infection.

L24 ANSWER 5 OF 6 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2002-091681 [13] WPIDS
DNC C2002-028502 [13]
TI **Tetravalent** vaccine for protection against **dengue**, comprising specific attenuated strains of all four viral serotypes
DC B04; D16
IN LANG J; SALUZZO J; SALUZZO J F
PA (AVET-C) AVENTIS PASTEUR
CYC 94
PIA EP 1159969 A1 20011205 (200213)* FR 8[0]
WO 2001091790 A1 20011206 (200213) FR
AU 2001067541 A 20011211 (200225) EN
BR 2001011223 A 20030401 (200327) PT
KR 2003007684 A 20030123 (200336) KO
CN 1431913 A 20030723 (200365) ZH
MX 2002011654 A1 20030301 (200413) ES
IN 2002001946 P4 20050211 (200539) EN
CN 1188168 C 20050209 (200622) ZH
ADT EP 1159969 A1 EP 2000-420112 20000530; IN 2002001946 P4 WO 2001-EP6871; AU 2001067541 A AU 2001-67541 20010529; BR 2001011223 A BR 2001-11223 20010529; CN 1431913 A CN 2001-810409 20010529; WO 2001091790 A1 WO 2001-EP6871 20010529; BR 2001011223 A WO 2001-EP6871 20010529; MX 2002011654 A1 WO 2001-EP6871 20010529; KR 2003007684 A KR 2002-715839 20021122; IN 2002001946 P4 IN 2002-CN1946 20021126; MX 2002011654 A1 MX 2002-11654 20021126; CN 1188168 C CN 2001-810409 20010529
FDT AU 2001067541 A Based on WO 2001091790 A; BR 2001011223 A Based on WO 2001091790 A; MX 2002011654 A1 Based on WO 2001091790 A
PRAI EP 2000-420112 20000530
AB EP 1159969 A1 UPAB: 20060118
NOVELTY - **Tetravalent** vaccine, (A), against **dengue** contains each of the attenuated strains deposited as CNCM I-2480, -2481, -2482 and -2483 (serotypes 1, 2, 3 and 4, respectively), with the quantity of the serotype 3 strain being lower than that of the other serotypes, is new.

ACTIVITY - Antiviral.

MECHANISM OF ACTION - Induction of an immune (antibody) response. A vaccine containing the four specified strains in ratio 3, 2, 1, 2 (where the figures represent the log10 values of the dilution of the virus needed to infect 50% of cells) was administered twice (0.5 ml) at an interval of 6 months. The geometric means of the titer of neutralizing antibodies 28 days after the second injection were 30.8; 91.9; 264 and 15.2, for serotypes 1, 2, 3 and 4, respectively. All subjects became seropositive for at least 3 serotypes and 75% for all four.

USE - (A) is used to protect against **dengue** virus infection.

ADVANTAGE - (A) is entirely safe, induces protection against all four serotypes and can be produced inexpensively on a large scale. Especially, reducing the quantity of the serotype 3 component greatly improves tolerance. In a trial, a vaccine containing equal amount of all four strains (log10 values of the dilution of the virus needed to infect 50% of cells = 4) produced a tolerance score (indicative of systemic side effects) of 27.4 for the first injection and 2.36 for the second. For a similar vaccine in which the level of serotype 3 component was reduced (log10 value of the dilution of this virus needed to infect 50% of cells = 1), the corresponding scores were 9.2 and 0.5.

L24 ANSWER 6 OF 6 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
Full Text
AN 2000-490499 [43] WPIDS
CR 2000-422855; 2000-422864; 2000-451903; 2000-611626; 2001-355218; 2002-750439; 2003-810761; 2003-810792; 2004-058613; 2004-280782; 2004-399242; 2004-460409; 2004-803905; 2005-010104; 2005-272417; 2005-561280; 2006-053824; 2006-076198; 2006-240155
DNC C2000-147296 [43]
DNN N2000-364019 [43]
TI Use of a steroid derivative for treatment and prevention of togavirus infection and/or its symptoms
DC A96; B05; C03; P31
IN AHLEM C N; FRINCKE J M; PRENDERGAST P T
PA (COLT-N) COLTHURST LTD; (HOLL-N) HOLLIS-EDEN PHARM; (HOLL-N) HOLLIS-EDEN

PHARM INC
CYC 88
PIA WO 2000032177 A2 20000608 (200043)* EN 99[0]
AU 2000031052 A 20000619 (200044) EN
BR 9915644 A 20010807 (200152) PT
EP 1133287 A2 20010919 (200155) EN
ZA 2001003847 A 20020130 (200217) EN 29
KR 2001101074 A 20011114 (200230) KO
JP 2002531397 W 20020924 (200278) JA 146
MX 2001005170 A1 20020401 (200363) ES
NZ 511721 A 20040730 (200454) EN
AU 775614 B2 20040805 (200474) EN
IL 142942 A 20060820 (200672) EN
ADT WO 2000032177 A2 WO 1999-US28082 19991124; BR 9915644 A BR 1999-15644 19991124; EP 1133287 A2 EP 1999-965050 19991124; NZ 511721 A NZ 1999-511721 19991124; BR 9915644 A WO 1999-US28082 19991124; EP 1133287 A2 WO 1999-US28082 19991124; JP 2002531397 W WO 1999-US28082 19991124; MX 2001005170 A1 WO 1999-US28082 19991124; NZ 511721 A WO 1999-US28082 19991124; AU 2000031052 A AU 2000-31052 19991124; AU 775614 B2 AU 2000-31052 19991124; JP 2002531397 W JP 2000-584873 19991124; ZA 2001003847 A ZA 2001-3847 20010511; MX 2001005170 A1 MX 2001-5170 20010523; KR 2001101074 A KR 2001-706525 20010524; IL 142942 A IL 1999-142942 19991124
FDT AU 775614 B2 Previous Publ AU 2000031052 A; AU 2000031052 A Based on WO 2000032177 A; BR 9915644 A Based on WO 2000032177 A; EP 1133287 A2 Based on WO 2000032177 A; JP 2002531397 W Based on WO 2000032177 A; MX 2001005170 A1 Based on WO 2000032177 A; NZ 511721 A Based on WO 2000032177 A; AU 775614 B2 Based on WO 2000032177 A; IL 142942 A Based on WO 2000032177 A
PRAI US 1999-126056P 19990323
US 1998-109924P 19981124
US 1999-124087P 19990311
AB WO 2000032177 A2 UPAB: 20060413
NOVELTY - A method for treatment and prevention of togavirus infection or reduction of one or more of the symptoms of togavirus infection comprises administration of steroid derivatives (I).

DETAILED DESCRIPTION - A method for treatment and prevention of togavirus infection or reduction of one or more of the symptoms of togavirus infection comprises administration of steroid derivatives of formula (I) or their salts, stereoisomers, positional isomers, metabolites, analogs, precursors, hydrates, tautomers, ionized forms and solvates.

Q1, Q5 = CO or C(R1)2;
Q2 = C(R1)2, C(R1)(Y), C(Y) or CH2CH2;
Q3 = H or C(R1)3;
Q4 = C(R1)2, CO, hydroxyvinylidene or methylmethylene;
X, Y = OH, H, lower alkyl, OCOR5, COOR5, halogen or O;
R1 = H, halogen, OH, 1-6C alkoxy or 1-6C alkyl;
R2 = H, OH, halogen, 1-6C alkyl, 1-6C alkoxy, OR3, ester, thioester, thioacetal, sulfate ester, sulfonate ester or carbamate; or
R1+R2 = O;
R3 = SO2OM, SO2OCH2CH(OCOR6)CH2OCOR6, P(O)(O)OCH2CH(OCOR7)CH2OCOR7, a glucuronide group of formula (a), 1-18C fatty acid, 2-10C alkynyl, (J)n-phenyl(1-5C alkyl) or (J)nphenyl(2-5C alkenyl) or 1-18C alkyl, 2-18C alkenyl, 1-18C ester or 1-18C thioester (all optionally substituted by ORpr, NHRpr or SRpr);
R5, R6 = 1-14C alkyl;
R7 = 1-14C alkyl or a group of formula (a);
Rpr = H or protecting group;
n = 0-3;
J = halogen, 1-4C alkyl, 2-4C alkenyl, 1-4C alkoxy, COOH, NO2, sulfate, sulfonyl, 1-6C carboxyl ester or 1-6C sulfate ester;
M = H, sodium, SO2OCH2CH(OCOR6)CH2OCOR6, P(O)(O)OCH2CH(OCOR7)CH2OCOR7 or a glucuronide group of formula (a); and
bonds a-d = single or double bonds, provided that b and c may not simultaneously be double bonds and that R1 groups are absent where necessary to make all carbons **tetravalent**.

INDEPENDENT CLAIMS are included for:
(1) enhancing the oral bioavailability of a therapeutic agent by administration of a plasma concentration enhancing compound; and
(2) treatment of prevention of a togavirus infection and/or reduction of one or more of the symptoms of togavirus infection, comprising administration of (I) in combination with 2-5 excipients selected from polyethylene glycol, dehydrated ethanol, benzyl benzoate, benzyl alcohol and propylene glycol, where the composition contains less

than 3% v/v (particularly less than 0.1% v/v) water.
ACTIVITY - Virucide; hepatotropic; anti-HIV.
MECHANISM OF ACTION - None given.
USE - For treatment and prevention of togavirus infection and/or its symptoms, particularly hepatitis C, hepatitis G, California encephalitis, St. Louis encephalitis, Western, Venezuelan or Eastern equine encephalitis, Colorado tick fever, LaCrosse encephalitis, Japanese encephalitis, yellow fever and Murray valley fever virus, GB virus A, B and C, **Dengue** virus 1-4, Semliki Forest virus, human rubella virus and bovine viral diarrhea virus, where the patient is optionally co-infected with a retrovirus (such as HIV) (claimed) or a second togavirus.
ADVANTAGE - Use of (I) gives improved patient response in treatment of hepatitis C infection while avoiding the side effects associated with interferon.

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=> d his

     (FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

     FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1          3111 S DENGUE
L2             6 S L1 AND 45AZ5
L3             6 S L2 AND PDK-27
L4            14 S L1 AND S16803
L5             9 S L4 NOT L2
L6             1 S L5 AND PDK-50
L7            12 S L1 AND CH53489
L8             7 S L7 NOT (L3 OR L6)
L9             0 S L8 AND PDK-20
L10            9 S L1 AND 341750
L11            4 S L10 NOT (L3 OR L6)
L12           95 S L1 AND TETRAVALENT
L13            2 S L12 AND TETRAVALENT/CLM
L14            1 S L13 NOT (L3 OR L5 OR L8)

     FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006
L15          551 S DENGUE
L16            2 S L15 AND 45AZ5
L17            2 S L15 AND S16803
L18            0 S L17 NOT L16
L19            1 S L15 AND CH53489
L20            1 S L19 NOT L16
L21            4 S L15 AND 341750
L22            2 S L21 NOT (L16 OR L17 OR L19)
L23            6 S L15 AND TETRAVALENT
L24            6 S L23 NOT (L16 OR L17 OR L19)

=> file medline
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                 ENTRY    SESSION
FULL ESTIMATED COST                              102.37     143.74

FILE 'MEDLINE' ENTERED AT 13:05:50 ON 29 DEC 2006

 FILE LAST UPDATED: 28 Dec 2006 (20061228/UP).  FILE COVERS 1950 TO DATE.

  All regular MEDLINE updates from November 15 to December 16 have been
  added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R))
  and 2007 tree numbers.

  The annual reload will be available in early 2007.

  This file contains CAS Registry Numbers for easy and accurate
  substance identification.

=> s dengue
L25         5433 DENGUE

=> s l25 and attenuate?
          96308 ATTENUATE?
L26         197 L25 AND ATTENUATE?

=> s l26 and (serial passage?)
          66580 SERIAL
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        43542 PASSAGE?
         2258 SERIAL PASSAGE?
                (SERIAL(W)PASSAGE?)
L27        19 L26 AND (SERIAL PASSAGE?)

=> s l27 and (primary kidney cells)
       618224 PRIMARY
       501577 KIDNEY
      1879509 CELLS
           33 PRIMARY KIDNEY CELLS
                (PRIMARY(W)KIDNEY(W)CELLS)
L28         5 L27 AND (PRIMARY KIDNEY CELLS)

=> d l28,cbib,ab,1-5

L28  ANSWER 1 OF 5     MEDLINE on STN
84304707.     PubMed ID: 6476216.   Selection of attenuated dengue 4 viruses
     by serial passage in primary kidney cells. V. Human response to
     immunization with a candidate vaccine prepared in fetal rhesus lung cells.
     Eckels K H; Scott R M; Bancroft W H; Brown J; Dubois D R; Summers P L;
     Russell P K; Halstead S B. The American journal of tropical medicine and
     hygiene, (1984 Jul) Vol. 33, No. 4, pp. 684-9. Journal code: 0370507.
     ISSN: 0002-9637. Pub. country: United States. Language: English.
AB   A dengue 4 (strain H241, PDK35-TD3 FRhL p3) vaccine attenuated by
     passage in primary dog kidney cells followed by passage and final vaccine
     preparation in DBS-FRhL-2 cells was tested in five yellow fever-immune
     volunteers. Only two volunteers seroconverted by producing
     hemagglutination-inhibiting and neutralizing antibodies. Mild illness,
     compatible with dengue infection was found only in the individuals who
     later developed antibodies. Both volunteers developed a rash by the 8th
     day following vaccination, coinciding with a slight elevation in
     temperature and leukopenia. Additionally, several serum enzymes were
     elevated during the observation period. Dengue 4 virus was isolated
     from the blood of the two infected volunteers starting as early as day 5
     post vaccination. During the viremic period, which lasted 5 days,
     phenotypically-changed virus was recovered, indicating genetic instability
     of the vaccine virus. The clinical disease and immune response in the two
     infected individuals was probably related to replication of the variant
     virus. Further testing of this vaccine in its present form is not
     indicated.

L28  ANSWER 2 OF 5     MEDLINE on STN
84304706.     PubMed ID: 6476215.   Selection of attenuated dengue 4 viruses
     by serial passage in primary kidney cells. IV. Characterization
     of a vaccine candidate in fetal rhesus lung cells. Halstead S B; Eckels K
     H; Putvatana R; Larsen L K; Marchette N J. The American journal of
     tropical medicine and hygiene, (1984 Jul) Vol. 33, No. 4, pp. 679-83.
     Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States.
     Language: English.
AB   A strain of primary dog kidney (PDK)-passaged dengue (DEN) 4 (H-241)
     virus cloned by terminal dilution (PDK 35-TD3) was propagated in large
     volumes in fetal rhesus lung (FRhL) cells to produce a candidate vaccine
     for evaluation in man. Production seed (FRhL p2) and candidate vaccine
     (FRhL p3) were subjected to rigorous safety tests to exclude contaminating
     microbial agents. There was no significant monkey neurovirulence of
     parental or PDK-passaged DEN-4 virus or of control fluid cultures.
     FRhL-passaged viruses retained the phenotypic characteristics: small
     (occasional medium) plaque; temperature sensitivity at 38.5 degrees C; and
     absence of plaque formation in African green monkey kidney cells,
     cytopathic effect in LLC-MK2 cells, and viral growth in human monocytes.
     FRhL p2 virus displayed low virulence for monkeys; only one of four
     animals was viremic and three of four developed low-titered antibody.
     FRhL p3 virus produced viremia in three monkeys and moderate to high
     hemagglutination-inhibition and neutralizing antibody titers in all
     animals. Virus at both passages in FRhL exhibited reduced neurovirulence
     in suckling mice as compared to parental DEN-4. Because of its safety and
     desirable monkey virulence attributes PDK 35-TD3 FRhL p3 is recommended
     for human phase I trial.

L28  ANSWER 3 OF 5     MEDLINE on STN
84304705.     PubMed ID: 6476214.   Selection of attenuated dengue 4 viruses
     by serial passage in primary kidney cells. III. Reversion to
     virulence by passage of cloned virus in fetal rhesus lung cells. Halstead
     S B; Marchette N J; Diwan A R; Palumbo N E; Putvatana R; Larsen L K. The
     American journal of tropical medicine and hygiene, (1984 Jul) Vol. 33, No.
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4, pp. 672-8. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Two strains of primary dog kidney-passaged **dengue** (DEN) 4 (H-241) virus cloned by terminal dilution (PDK 24-TD3 and 35-TD3) were propagated in fetal rhesus lung (FRhL) cells to produce candidate vaccine virus seeds. Both **serial passage** and prolonged replication of PDK 24-TD3 in FRhL resulted in appearance of medium and large plaques in LLC-MK2 assays. When picked, these plaques proved to contain temperature-resistant, monkey-virulent revertants. **Serial passage** and prolonged replication of PDK 24-TD3 in LLC-MK2 cells did not result in reversion; but, prolonged replication in PDK cells did. Passage of PDK 35-TD3 in FRhL cells resulted in appearance of medium size plaques which, when picked, yielded temperature sensitive (ts) (38.5 degrees C) viruses of low monkey-virulence. Because of its stability in monkeys and FRhL cells, reduced monkey virulence and ts property. PDK 35-TD3 is a promising candidate for trial in man.

L28 ANSWER 4 OF 5 MEDLINE on STN

84304704. PubMed ID: 6476213. Selection of **attenuated dengue** 4 viruses by **serial passage** in **primary kidney cells**. II. Attributes of virus cloned at different dog kidney passage levels. Halstead S B; Marchette N J; Diwan A R; Palumbo N E; Putvatana R. The American journal of tropical medicine and hygiene, (1984 Jul) Vol. 33, No. 4, pp. 666-71. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Uncloned **dengue** (DEN) 4 (H-241) which had been passaged 15, 30 and 50 times in primary dog kidney (PDK) cells were subjected to two successive terminal dilution procedures. In the first (3Cl), virus was diluted in 10-fold steps in 10 replicate tubes. An infected tube from a dilution row with three or fewer virus-infected tubes was selected for two further passages. In the second (TD3), virus was triple terminal diluted using 2-fold dilution steps and selecting one positive tube out of 10. Both procedures selected virus population which differed from antecedents. Plaque size of PDK 15 was medium, PDK 30, small and PDK 50, pin-point. PDK 19-3Cl were medium and 56-3Cl, 24-TD3, 35-TD3 and 61-TD3 were all small. All cloned virus replication was completely shut-off at 38.5 degrees C; PDK 15 and 30 continued to replicate at this temperature. Uncloned viruses showed a graduated decrease in monkey virulence with PDK passage; cloned viruses were either avirulent for monkeys (19-3Cl, 56-31Cl, 24-TD3 and 35-TD3) or produced revertant large plaque parental-type viremia (35-3Cl and 61-TD3). Those cloned viruses which exhibited temperature sensitivity, reduced monkey virulence and stability after monkey passage may be suitable as vaccine candidates for evaluation in human beings.

L28 ANSWER 5 OF 5 MEDLINE on STN

84304703. PubMed ID: 6476212. Selection of **attenuated dengue** 4 viruses by **serial passage** in **primary kidney cells**. I. Attributes of uncloned virus at different passage levels. Halstead S B; Diwan A R; Marchette N J; Palumbo N E; Srisukonth L. The American journal of tropical medicine and hygiene, (1984 Jul) Vol. 33, No. 4, pp. 654-65. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Attempts were made to **attenuate** prototype **dengue** (DEN) 4 (H-241) virus. The original viremic human serum was passed once in a susceptible monkey and twice in Aedes albopictus mosquitoes and then serially passed in primary dog kidney (PDK) and African green monkey kidney (GMK) cells. Weekly transfers of undiluted virus were carried to the 50th passage in both primary cell cultures. Biological markers were studied at passages 7, 15, 30 and 50. Parental DEN-4 phenotype characteristics included large plaque formation in LLC-MK2 cells, plaque formation in GMK cells, cytopathic effect in LLC-MK2 cells, growth in human monocyte cultures, growth at 39 degrees C, consistent production of viremia in monkeys and short-incubation neurovirulence in mice. At the seventh passage in both PDK and GMK cell cultures, DEN-4 viruses exhibited reduced plaque-size in LLC-MK2, and failed to plaque in GMK, to produce cytopathic effect in LLC-MK2, or to grow in human monocytes. **Serial passage** in PDK, as opposed to GMK, resulted in a graduated loss of monkey virulence. Rhesus monkeys inoculated with the PDK 50 strain failed to develop detectable viremia and only 1 of 4 developed an antibody response. Also, replication of PDK 50 was completely shut-off at 39 degrees C. The graduated change in biological properties noted, particularly those in PDK cells, provide a range of potential vaccine candidates for evaluation in human beings.

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=> d his

     (FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

     FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1          3111 S DENGUE
L2             6 S L1 AND 45AZ5
L3             6 S L2 AND PDK-27
L4            14 S L1 AND S16803
L5             9 S L4 NOT L2
L6             1 S L5 AND PDK-50
L7            12 S L1 AND CH53489
L8             7 S L7 NOT (L3 OR L6)
L9             0 S L8 AND PDK-20
L10            9 S L1 AND 341750
L11            4 S L10 NOT (L3 OR L6)
L12           95 S L1 AND TETRAVALENT
L13            2 S L12 AND TETRAVALENT/CLM
L14            1 S L13 NOT (L3 OR L5 OR L8)

     FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006
L15          551 S DENGUE
L16            2 S L15 AND 45AZ5
L17            2 S L15 AND S16803
L18            0 S L17 NOT L16
L19            1 S L15 AND CH53489
L20            1 S L19 NOT L16
L21            4 S L15 AND 341750
L22            2 S L21 NOT (L16 OR L17 OR L19)
L23            6 S L15 AND TETRAVALENT
L24            6 S L23 NOT (L16 OR L17 OR L19)

     FILE 'MEDLINE' ENTERED AT 13:05:50 ON 29 DEC 2006
L25         5433 S DENGUE
L26          197 S L25 AND ATTENUATE?
L27           19 S L26 AND (SERIAL PASSAGE?)
L28            5 S L27 AND (PRIMARY KIDNEY CELLS)

=> s l27 and (primary dog kidney)
        618224 PRIMARY
         82933 DOG
        501577 KIDNEY
            28 PRIMARY DOG KIDNEY
                 (PRIMARY(W)DOG(W)KIDNEY)
L29         12 L27 AND (PRIMARY DOG KIDNEY)

=> s l29 not l28
L30          7 L29 NOT L28

=> d l30,cbib,ab,1-7

L30  ANSWER 1 OF 7     MEDLINE on STN
2004040702.    PubMed ID: 14740951.   Phase 1 studies of Walter Reed Army
     Institute of Research candidate attenuated dengue vaccines: selection
     of safe and immunogenic monovalent vaccines. Kanesa-Thasan N; Edelman R;
     Tacket C O; Wasserman S S; Vaughn D W; Coster T S; Kim-Ahn G J; Dubois D
     R; Putnak J R; King A; Summers P L; Innis B L; Eckels K H; Hoke C H Jr.
     (Walter Reed Army Institute of Research, Washington, District of Columbia,
     USA.. niranjan.kanesa-thasan@det.amedd.army.mil) . The American journal of
     tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 17-23.
     Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States.
     Language: English.
AB   We describe the results of initial safety testing of 10 live-attenuated
     dengue virus (DENV) vaccine candidates modified by serial passage in
     primary dog kidney (PDK) cells at the Walter Reed Army Institute of
     Research. The Phase 1 studies, conducted in 65 volunteers, were designed
     to select an attenuated vaccine candidate for each DENV serotype. No
     recipient of the DENV candidate vaccines sustained serious injury or
     required treatment. Three vaccine candidates were associated with
     transient idiosyncratic reactions in one volunteer each, resulting in
     their withdrawal from further clinical development. Increasing PDK cell
     passage of DENV-1, DENV-2, and DENV-3 candidate vaccines increased
     attenuation for volunteers, yet also decreased infectivity and
     immunogenicity. This effect was less clear for DENV-4 candidate vaccines
     following 15 and 20 PDK cell passages. Only one passage level each of the
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tested DENV-2, -3, and -4 vaccine candidates was judged acceptably reactogenic and suitable for expanded clinical study. Subsequent studies with more recipients will further establish safety and immunogenicity of the four selected vaccine candidates: DENV-1 45AZ5 PDK 20, DENV-2 S16803 PDK 50, DENV-3 CH53489 PDK 20, and DENV-4 341750 PDK 20.

L30 ANSWER 2 OF 7 MEDLINE on STN

2004040701. PubMed ID: 14740950. Modification of **dengue** virus strains by passage in **primary dog kidney** cells: preparation of candidate vaccines and immunization of monkeys. Eckels Kenneth H; Dubois Doria R; Putnak Robert; Vaughn David W; Innis Bruce L; Henchal Erik A; Hoke Charles H Jr. (Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, Silver Spring, Maryland 20910, USA.) The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 12-6. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB **Dengue** (DENV) virus strains for each of the four DENV serotypes were modified by passage in **primary dog kidney** (PDK) cell cultures with final manufacture of vaccine lots in fetal rhesus monkey diploid cell cultures. "Strain sets" consisting of serially-passaged DENV were inoculated in rhesus monkeys along with unmodified parent viruses for each strain. Vaccine candidates were compared with unmodified parent viruses by measuring viremia and immune responses. All except one DENV-1 strain demonstrated reduced infection in monkeys after PDK cell passage. A DENV-3 strain lost all monkey infectivity after PDK cell passage. Twelve vaccine candidates were selected for Phase 1 human trials through this selection process.

L30 ANSWER 3 OF 7 MEDLINE on STN

2004040700. PubMed ID: 14740949. Biologic properties of **dengue** viruses following **serial passage** in **primary dog kidney** cells: studies at the University of Hawaii: Halstead Scott B; Marchette Nyven J. (Department of Tropical Medicine and Medical Microbiology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, Hawaii, USA.. halsteads@erols.com) . The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 5-11. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB **Serial passage** at low dilution of seven different wild-type **dengue** (DEN) viruses into **primary dog kidney** (PDK) cell cultures placed selective pressure that resulted in the following changes from parental phenotype: smaller plaques in LLC-MK2 cells, absent plaque formation in green monkey kidney cells, lack of a cytopathic effect in LLC-MK2 cells, shut-off of virus replication at high temperatures (temperature sensitivity), reduced virulence for rhesus monkeys manifested by reduced or absent viremia and/or absence of a secondary-type antibody response following homotypic challenge, and progressive increase in the mean day of death following intracerebral inoculation of sucking mice. Two DEN-1 strains showed most of these changes by the 15th PDK passage. Only one of two DEN-2 strains studied was carried to the 50th PDK passage at the University of Hawaii. For the latter strain, both the temperature of viral replicative shutoff and mouse neurovirulence were reduced. Three DEN-4 strains showed similar late-passage biologic marker changes. The observations made, although not exhaustive, provide laboratory correlates for virus strains that have shown reduced virulence but retained immunogenicity in humans. Candidate human vaccines have been prepared from five of the studied strains: DEN-1 (16007) at PDK 13, DEN-2 (16681 and S-16803) at PDK 50 or above, and DEN-4 (1036 and 341750) at PDK 48 and 20, respectively.

L30 ANSWER 4 OF 7 MEDLINE on STN

2001253021. PubMed ID: 11285157. Study of biologic attributes of Cuban **dengue** 2 virus after **serial passage** in **primary dog kidney** cells. Alvarez M; Guzman M G; Pupo M; Morier L; Bravo J; Rodriguez R. (Department of Virology, PAHO/WHO Collaborator Center for Viral Diseases, Tropical Medicine Institute of Havana, Cuba.) International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases, (2001) Vol. 5, No. 1, pp. 35-9. Journal code: 9610933. ISSN: 1201-9712. Pub. country: Canada. Language: English.

AB OBJECTIVE: The **serial passage** of **dengue** viruses in **primary dog kidney** (PDK) cells has resulted in selection of **attenuated** viruses. However, the molecular changes responsible for loss of virulence are not well characterized. This article describes the isolation and biologic attributes of one **dengue** 2 virulent strain as a first step to allow the study of determinants of virulence at the molecular level. METHODS: A15 **dengue** 2 Cuban strain was isolated from the viremic plasma of a patient

with uncomplicated **dengue** fever during the 1981 epidemic. This was then subjected to **serial passage** in PDK cells. Viruses resulting from several PDK passages were compared to the parent strain for plaque size and temperature sensitivity, neurovirulence in newborn mice, and cytopathogenic effects on LLC-MK(2) and C6/36-HT cell lines. RESULTS: A15 **dengue** 2 Cuban strain was successfully propagated in PDK cells. **Primary dog kidney** 52 to 53 viruses exhibited several biologic attributes, such as small plaques, temperature sensitivity, reduced mouse neurovirulence, and cytopathic effect in permissive cell lines. CONCLUSIONS: These results represent the first step to allow attenuation of this strain of **dengue** 2 virus.

L30 ANSWER 5 OF 7 MEDLINE on STN
2000407920. PubMed ID: 10821973. Live **attenuated** tetravalent **dengue** vaccine. Bhamarapravati N; Sutee Y. (Institute of Science and Technology for Research and Development, Mahidol University, Salaya, Thailand.) Vaccine, (2000 May 26) Vol. 18 Suppl 2, pp. 44-7. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The development of a live **attenuated** tetravalent **dengue** vaccine is currently the best strategy to obtain a vaccine against **dengue** viruses. The Mahidol University group developed candidate live **attenuated** vaccines by attenuation through **serial passages** in certified primary cell cultures. **Dengue** serotype 1, 2 and 4 viruses were developed in **primary dog kidney** cells, whereas **dengue** serotype 3 was serially passaged in primary African green monkey kidney cells. Tissue culture passaged strain viruses were subjected to biological marker studies. Candidate vaccines have been tested as monovalent (single virus), bivalent (two viruses), trivalent (three viruses) and tetravalent (all four serotype viruses) vaccines in Thai volunteers. They were found to be safe and immunogenic in both adults and children. The Mahidol live **attenuated dengue** 2 virus was also tested in American volunteers and resulted in good immune response indistinguishable from those induced in Thai volunteers. The master seeds from the four live **attenuated** virus strains developed were provided to Pasteur Merieux Connaught of France for production on an industrial scale following good manufacturing practice guidelines.

L30 ANSWER 6 OF 7 MEDLINE on STN
97437483. PubMed ID: 9292016. Molecular analysis of **dengue** virus attenuation after **serial passage** in **primary dog kidney** cells. Puri B; Nelson W M; Henchal E A; Hoke C H; Eckels K H; Dubois D R; Porter K R; Hayes C G. (Infectious Diseases Department, Naval Medical Research Institute, Bethesda, Maryland 20889-5607, USA.. PURI@MAIL2.NMRI.NNMC.NAVY.MIL) . The Journal of general virology, (1997 Sep) Vol. 78 (Pt 9), pp. 2287-91. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.
AB The complete nucleotide sequences of the genomes of **dengue**-1 virus virulent 45AZ5 PDK-0 and **attenuated** vaccine candidate strain 45AZ5 PDK-27 have been determined and compared with the **dengue**-1 virus Western Pacific (West Pac) 74 parent strain from which 45AZ5 PDK-0 was derived. Twenty-five (0.23%) nucleotide and 10 (0.29%) amino acid substitutions occurred between parent strain **dengue**-1 virus West Pac 74 and virulent strain 45AZ5 PDK-0, which was derived from the parent by **serial passage** in diploid foetal rhesus lung (FRhL-2) and mutagenized with 5-azacytidine. These substitutions were preserved in the 45AZ5 PDK-27 vaccine. 45AZ5 PDK-0 and PDK-27 strains, which differ by 27 passages in **primary dog kidney** (PDK) cells, show 25 (0.23%) nucleotide and 11 (0.32%) amino acid divergences. These comparative studies suggest that the changes which occurred between the West Pac 74 and 45AZ5 PDK-0 strains may alter the biological properties of the virus but may not be important for attenuation. Important nucleotide base changes responsible for attenuation accumulated between 45AZ5 PDK-0 and 27.

L30 ANSWER 7 OF 7 MEDLINE on STN
95088425. PubMed ID: 7995984. A live **attenuated dengue**-1 vaccine candidate (45AZ5) passaged in **primary dog kidney** cell culture is **attenuated** and immunogenic for humans. Edelman R; Tacket C O; Wasserman S S; Vaughn D W; Eckels K H; Dubois D R; Summers P L; Hoke C H. (Department of Medicine, University of Maryland School of Medicine, Baltimore 21201.) The Journal of infectious diseases, (1994 Dec) Vol. 170, No. 6, pp. 1448-55. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.
AB A **dengue**-1 candidate vaccine (45AZ5), previously found to be underattenuated in 2 volunteers, was further **attenuated** by passage in **primary dog kidney** (PDK) cell cultures. New candidate vaccines

prepared from three levels of PDK-passaged virus, PDK-10, PDK-20, and PDK-27, were each injected into 9 or 10 volunteers. There was a significant, progressive decline in viremia, clinical illness, and hematologic changes from low to high PDK cell passage level. PDK-20 infected all 10 vaccinees and induced viremia in 5, transient fever in 3, symptoms that resulted in curtailed activities for < or = 1 day in 4, and neutralizing antibody in all 10, which persisted for > or = 1 year in 5 of 8 vaccinees tested. Progressive passage in PDK cell culture progressively **attenuates** vaccine candidate strain 45AZ5 for humans. Because passage level PDK-20 may be suitable for healthy adults at high risk of **dengue** fever, additional clinical trials of this strain are warranted.

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=> d his

     (FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

     FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1          3111 S DENGUE
L2             6 S L1 AND 45AZ5
L3             6 S L2 AND PDK-27
L4            14 S L1 AND S16803
L5             9 S L4 NOT L2
L6             1 S L5 AND PDK-50
L7            12 S L1 AND CH53489
L8             7 S L7 NOT (L3 OR L6)
L9             0 S L8 AND PDK-20
L10            9 S L1 AND 341750
L11            4 S L10 NOT (L3 OR L6)
L12           95 S L1 AND TETRAVALENT
L13            2 S L12 AND TETRAVALENT/CLM
L14            1 S L13 NOT (L3 OR L5 OR L8)

     FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006
L15          551 S DENGUE
L16            2 S L15 AND 45AZ5
L17            2 S L15 AND S16803
L18            0 S L17 NOT L16
L19            1 S L15 AND CH53489
L20            1 S L19 NOT L16
L21            4 S L15 AND 341750
L22            2 S L21 NOT (L16 OR L17 OR L19)
L23            6 S L15 AND TETRAVALENT
L24            6 S L23 NOT (L16 OR L17 OR L19)

     FILE 'MEDLINE' ENTERED AT 13:05:50 ON 29 DEC 2006
L25         5433 S DENGUE
L26          197 S L25 AND ATTENUATE?
L27           19 S L26 AND (SERIAL PASSAGE?)
L28            5 S L27 AND (PRIMARY KIDNEY CELLS)
L29           12 S L27 AND (PRIMARY DOG KIDNEY)
L30            7 S L29 NOT L28

=> e eckels k/au
E1             1     ECKELS J/AU
E2             1     ECKELS J A/AU
E3             1 --> ECKELS K/AU
E4            55     ECKELS K H/AU
E5             8     ECKELS KENNETH H/AU
E6             1     ECKELS PHILLIP/AU
E7             8     ECKELS R/AU
E8             5     ECKELS T/AU
E9             1     ECKELS T J/AU
E10            4     ECKELT A/AU
E11            1     ECKELT BIRGIT/AU
E12            1     ECKELT D/AU

=> s e5
L31            8 "ECKELS KENNETH H"/AU

=> s l31 and dengue
          5433 DENGUE
L32            7 L31 AND DENGUE

=> d l32,cbib,ab,1-7
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L32 ANSWER 1 OF 7 MEDLINE on STN

2006272777. PubMed ID: 16703509. Protection of Rhesus monkeys against **dengue** virus challenge after tetravalent live attenuated **dengue** virus vaccination. Sun Wellington; Nisalak Ananda; Gettayacamin Montip; **Eckels Kenneth H**; Putnak J Robert; Vaughn David W; Innis Bruce L; Thomas Stephen J; Endy Timothy P. (Department of Virus Diseases, Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, Silver Spring, Maryland 20910-7500, USA.. wellinton.sun@us.army.mil) . The Journal of infectious diseases, (2006 Jun 15) Vol. 193, No. 12, pp. 1658-65. Electronic Publication: 2006-05-09. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Rhesus monkeys develop viremia after **dengue** virus (DENV) inoculation and have been used as an animal model to study DENV infection and DENV vaccine candidates. We evaluated, in this model, the protective efficacy of a live attenuated tetravalent DENV vaccine (TDV) candidate against parenteral challenge with parental near-wild-type DENV strains. Twenty monkeys were vaccinated with TDV at 0 and 1 month, and 20 unvaccinated monkeys served as controls. Vaccinated animals and their controls were inoculated with 10(3)-10(4) pfu of challenge virus 4.5 months after the second vaccination. Primary vaccination resulted in 95%, 100%, 70%, and 15% seroconversion to DENV serotypes 1, 2, 3, and 4 (DENV-1, -2, -3, and -4), respectively. After the second vaccination, the seropositivity rates were 100%, 100%, 90%, and 70%, respectively. Vaccination with TDV resulted in complete protection against viremia from DENV-2 challenge and in 80%, 80%, and 50% protection against challenge with DENV-1, -3, and -4, respectively. Our results suggest that the TDV can elicit protective immunity against all 4 DENV serotypes. Interference among the 4 vaccine viruses may have resulted in decreased antibody responses to DENV-3 and -4, which would require reformulation or dose optimization to minimize this interference during testing of the vaccine in humans.

L32 ANSWER 2 OF 7 MEDLINE on STN

2005354017. PubMed ID: 16005749. An evaluation of **dengue** type-2 inactivated, recombinant subunit, and live-attenuated vaccine candidates in the rhesus macaque model. Robert Putnak J; Coller Beth-Ann; Voss Gerald; Vaughn David W; Clements David; Peters Iain; Bignami Gary; Houng Hou-Shu; Chen Robert C-M; Barvir David A; Seriwatana Jitvimol; Cayphas Sylvie; Garcon Nathalie; Gheysen Dirk; Kanesa-Thasan Niranjan; McDonell Mike; Humphreys Tom; **Eckels Kenneth H**; Prieels Jean-Paul; Innis Bruce L. (Walter Reed Army Institute of Research, Division of Communicable Diseases and Immunology, 503 Robert Grant Avenue, Silver Spring, MD 20910, USA.. robert.putnak@na.amedd.army.mil) . Vaccine, (2005 Aug 15) Vol. 23, No. 35, pp. 4442-52. Journal code: 8406899. ISSN: 0264-410X. Pub. country: Netherlands. Language: English.

AB The safety, immunogenicity, and protective efficacy of two non-replicating antigen-based vaccines and one live-attenuated virus (LAV) vaccine for **dengue** type-2 (**dengue**-2) virus were evaluated in the rhesus macaque model. The non-replicating vaccines consisted of whole, purified inactivated virus (PIV) and a recombinant subunit protein containing the amino-(N)-terminal 80% of envelope protein (r80E), each formulated with one of five different adjuvants. Each formulation was administered to three animals on a 0, 3-month schedule. Following the primary immunizations, 37 of 39 animals demonstrated **dengue**-2 virus neutralizing antibodies. After the booster immunizations all animals had **dengue** neutralizing antibodies with peak titers ranging from 1:100 to 1:9700. The highest neutralizing antibody titers were observed in the groups that received r80E antigen formulated with AS04, AS05, or AS08 adjuvant, and PIV formulated with AS05 or AS08 adjuvant. These newer adjuvants are based on alum, fraction QS-21 of saponin, and monophosphoryl lipid A (MPL). Protection was evaluated by **dengue**-2 virus challenge 2 months after the booster by the measurement of circulating virus (viremia) and post-challenge immune responses. Several groups exhibited nearly complete protection against viremia by bioassay, although there was evidence for challenge virus replication by Taqmantrade mark and immunological assays. None of the vaccines conferred sterile immunity.

L32 ANSWER 3 OF 7 MEDLINE on STN

2004054861. PubMed ID: 14756126. Progress in development of a live-attenuated, tetravalent **dengue** virus vaccine by the United States Army Medical Research and Materiel Command. Innis Bruce L; **Eckels Kenneth H**. The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 1-4. Ref: 32. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

L32 ANSWER 4 OF 7 MEDLINE on STN

2004040706. PubMed ID: 14740955. Phase I trial of 16 formulations of a tetravalent live-attenuated **dengue** vaccine. Edelman Robert; Wasserman Steven S; Bodison Sacared A; Putnak Robert J; **Eckels Kenneth H**; Tang Douglas; Kanesa-Thasan Niranjan; Vaughn David W; Innis Bruce L; Sun Wellington. (Department of Medicine and the Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.. redelman@medicine.umaryland.edu) . The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 48-60. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Laboratory-attenuated strains of each of the four **dengue** serotypes previously tested as monovalent vaccines in volunteers were combined and tested for immunogenicity, safety, and reactogenicity in 16 dosage combinations. Tetravalent vaccines made using combinations of high (10(5-6) plaque-forming units [PFU]/dose) or low (10(3.5-4.5) PFU/dose) dosage formulations of each of the four viruses were inoculated in 64 flavivirus non-immune adult volunteers to determine which, if any, formulation raised neutralizing antibodies in at least 75% of volunteers to at least three of four **dengue** serotypes following one or two inoculations. Such formulations, if safe and sufficiently non-reactogenic, would be considered for an expanded Phase II trial in the future. Formulations 1-15 were each inoculated into three or four volunteers (total = 54) on days 0 and 28. Formulation 16 was tested in 10 volunteers, five volunteers inoculated on days 0 and 30, one volunteer on days 0 and 120, and four volunteers on days 0, 30, and 120. Blood was drawn for serologic assays immediately before and one month after each vaccination, and for viremia assay on day 10 after each vaccination. The 16 formulations were safe, but variably reactogenic after the first vaccination, and nearly non-reactogenic after the second and third vaccinations. Reactogenicity was positively correlated with immunogenicity. *Similar proportions of volunteers seroconverted* to **dengue**-1 (69%), **dengue**-2 (78%), and **dengue**-3 (69%), but significantly fewer volunteers seroconverted to **dengue**-4 (38%). The geometric mean 50% plaque reduction neutralization test titers in persons who seroconverted were significantly higher to **dengue**-1 (1:94) than to **dengue**-2 (1:15), **dengue**-3 (1:10), and **dengue**-4 (1:2). Seven formulations met the serologic criteria required for an expanded trial, and three of these were sufficiently attenuated clinically to justify further testing.

L32 ANSWER 5 OF 7 MEDLINE on STN

2004040703. PubMed ID: 14740952. Vaccination of human volunteers with monovalent and tetravalent live-attenuated **dengue** vaccine candidates. Sun Wellington; Edelman Robert; Kanesa-Thasan Niranjan; **Eckels Kenneth H**; Putnak J Robert; King Alan D; Houng Huo-Shu; Tang Douglas; Scherer John M; Hoke Charles H Jr; Innis Bruce L. (Department of Virus Diseases, Walter Reed Army Institute of Research, Silver Spring, Maryland 20910, USA.. wellington.sun@na.amedd.army.mil) . The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 24-31. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Four serotypes of monovalent live attenuated **dengue** virus vaccine candidates were tested for reactogenicity and immunogenicity in 49 flavivirus non-immune adult human volunteers. The four monovalent candidates were then combined into a tetravalent formulation and given to another 10 volunteers. Neutralizing antibody seroconversion rates after a single-dose monovalent vaccination ranged from 53% to 100%. Solicited reactogenicity was scored by each volunteer. A composite index, the Reactogenicity Index, was derived by these self-reported scores. Reactogenicity differed among the four serotype candidates with serotype-1 associated with the most vaccine related side effects. A second dose of monovalent vaccines at either 30 days or 90 days was much less reactogenic but did not significantly increase seroconversion rates. Seroconversion rates in the 10 volunteers who received a single dose of tetravalent vaccine ranged from 30% to 70% among the four serotypes. Similar to the monovalent vaccines, a second dose of the tetravalent vaccine at one month was less reactogenic and did not increase seroconversion. A third dose of the tetravalent vaccine at four months resulted in three of four volunteers with trivalent or tetravalent high-titer neutralizing antibody responses.

L32 ANSWER 6 OF 7 MEDLINE on STN

2004040701. PubMed ID: 14740950. Modification of **dengue** virus strains by passage in primary dog kidney cells: preparation of candidate vaccines and

immunization of monkeys. **Eckels Kenneth H**; Dubois Doria R; Putnak Robert; Vaughn David W; Innis Bruce L; Henchal Erik A; Hoke Charles H Jr. (Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, Silver Spring, Maryland 20910, USA.) The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 12-6. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB **Dengue** (DENV) virus strains for each of the four DENV serotypes were modified by passage in primary dog kidney (PDK) cell cultures with final manufacture of vaccine lots in fetal rhesus monkey diploid cell cultures. "Strain sets" consisting of serially-passaged DENV were inoculated in rhesus monkeys along with unmodified parent viruses for each strain. Vaccine candidates were compared with unmodified parent viruses by measuring viremia and immune responses. All except one DENV-1 strain demonstrated reduced infection in monkeys after PDK cell passage. A DENV-3 strain lost all monkey infectivity after PDK cell passage. Twelve vaccine candidates were selected for Phase 1 human trials through this selection process.

L32 ANSWER 7 OF 7 MEDLINE on STN

2004017651. PubMed ID: 14714438. Formalin-inactivated whole virus and recombinant subunit flavivirus vaccines. **Eckels Kenneth H**; Putnak Robert. (Division of Communicable Diseases and Immunology, Walter Reed Army Institute of Research, Silver Spring, Maryland 20910, USA.) Advances in virus research, (2003) Vol. 61, pp. 395-418. Ref: 84. Journal code: 0370441. ISSN: 0065-3527. Pub. country: United States. Language: English.

AB The Flaviviridae is a family of arthropod-borne, enveloped, RNA viruses that contain important human pathogens such as yellow fever (YF), Japanese encephalitis (JE), tick-borne encephalitis (TBE), West Nile (WN), and the **dengue** (DEN) viruses. Vaccination is the most effective means of disease prevention for these viral infections. A live-attenuated vaccine for YF, and inactivated vaccines for JE and TBE have significantly reduced the incidence of disease for these viruses, while licensed vaccines for DEN and WN are still lacking despite a significant disease burden associated with these infections. This review focuses on inactivated and recombinant subunit vaccines (non-replicating protein vaccines) in various stages of laboratory development and human testing. A purified, inactivated vaccine (PIV) candidate for DEN will soon be evaluated in a phase 1 clinical trial, and a second-generation JE PIV produced using similar technology has advanced to phase 2/3 trials. The inactivated TBE vaccine used successfully in Europe for almost 30 years continues to be improved by additional purification, new stabilizers, an adjuvant, and better immunization schedules. The recent development of an inactivated WN vaccine for domestic animals demonstrates the possibility of producing a similar vaccine for human use. Advances in flavivirus gene expression technology have led to the production of several recombinant subunit antigen vaccine candidates in a variety of expression systems. Some of these vaccines have shown sufficient promise in animal models to be considered as candidates for evaluation in clinical trials. Feasibility of non-replicating flavivirus vaccines has been clearly demonstrated and further development is now warranted.

=> d his

(FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006

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L1         3111 S DENGUE
L2            6 S L1 AND 45AZ5
L3            6 S L2 AND PDK-27
L4           14 S L1 AND S16803
L5            9 S L4 NOT L2
L6            1 S L5 AND PDK-50
L7           12 S L1 AND CH53489
L8            7 S L7 NOT (L3 OR L6)
L9            0 S L8 AND PDK-20
L10           9 S L1 AND 341750
L11           4 S L10 NOT (L3 OR L6)
L12          95 S L1 AND TETRAVALENT
L13           2 S L12 AND TETRAVALENT/CLM
L14           1 S L13 NOT (L3 OR L5 OR L8)
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FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006

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L15         551 S DENGUE
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L16           2 S L15 AND 45AZ5
L17           2 S L15 AND S16803
L18           0 S L17 NOT L16
L19           1 S L15 AND CH53489
L20           1 S L19 NOT L16
L21           4 S L15 AND 341750
L22           2 S L21 NOT (L16 OR L17 OR L19)
L23           6 S L15 AND TETRAVALENT
L24           6 S L23 NOT (L16 OR L17 OR L19)

    FILE 'MEDLINE' ENTERED AT 13:05:50 ON 29 DEC 2006
L25        5433 S DENGUE
L26         197 S L25 AND ATTENUATE?
L27          19 S L26 AND (SERIAL PASSAGE?)
L28           5 S L27 AND (PRIMARY KIDNEY CELLS)
L29          12 S L27 AND (PRIMARY DOG KIDNEY)
L30           7 S L29 NOT L28
              E ECKELS K/AU
L31           8 S E5
L32           7 S L31 AND DENGUE

=> e putnak j r/au
E1            2     PUTMANS PASCALE/AU
E2            1     PUTNA L/AU
E3           19 --> PUTNAK J R/AU
E4            2     PUTNAK J ROBERT/AU
E5           10     PUTNAK R/AU
E6            6     PUTNAK ROBERT/AU
E7            1     PUTNAK ROBERT J/AU
E8            6     PUTNAM A/AU
E9            1     PUTNAM A D/AU
E10           6     PUTNAM A H/AU
E11           4     PUTNAM A J/AU
E12           2     PUTNAM A L/AU

=> s e3-e4
             19 "PUTNAK J R"/AU
              2 "PUTNAK J ROBERT"/AU
L33          21 ("PUTNAK J R"/AU OR "PUTNAK J ROBERT"/AU)

=> s 133 and dengue
          5433 DENGUE
L34         11 L33 AND DENGUE

=> s l34 not l31
L35          9 L34 NOT L31

=> d 135,cbib,ab,1-9

L35  ANSWER 1 OF 9     MEDLINE on STN
2004040704.    PubMed ID: 14740953.   Atypical antibody responses in dengue
     vaccine recipients. Kanesa-Thasan N; Sun W; Ludwig G V; Rossi C; Putnak J
     R; Mangiafico J A; Innis B L; Edelman R. (Walter Reed Army Institute of
     Research, Washington, District of Columbia, USA.. niranjan.kanesa-
     thasan@det.amedd.army.mil) . The American journal of tropical medicine and
     hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 32-8.  Journal code:
     0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.
AB   Eight of 69 (12%) healthy adult volunteers vaccinated with monovalent
     live-attenuated dengue virus (DENV) vaccine candidates had atypical
     antibody responses, with depressed IgM:IgG antibody ratios and induction
     of high-titer hemagglutination-inhibiting and neutralizing (NT) antibodies
     to all four DENV serotypes.  These features suggested flavivirus exposure
     prior to DENV vaccination, yet no volunteer had a history of previous
     flavivirus infection, flavivirus vaccination, or antibody to flaviviruses
     evident before DENV vaccination.  Moreover, production of antibody to DENV
     by atypical responders (AR) was not accelerated compared with antibody
     responses in the 61 flavivirus-naive responders (NR).  Further evaluation
     revealed no differences in sex, age, race, DENV vaccine candidate
     received, or clinical signs and symptoms following vaccination between AR
     and NR.  However, viremia was delayed at the onset in AR compared with NR.
     A comparative panel of all AR and five randomly selected NR found
     flavivirus cross-reactive antibody after vaccination only in AR.
     Unexpectedly, six of eight AR had NT antibodies to yellow fever virus
     (YFV) > 1:10 before vaccination while NR had none (P = 0.04).  The AR also
     universally demonstrated YFV NT antibody titers > or = 1:160 after DENV
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vaccination, whereas four of five NR failed to seroconvert (P = 0.02). Yellow fever virus priming broadens the antibody response to monovalent DENV vaccination. The effect of flavivirus priming on the clinical and immunologic response to tetravalent DENV vaccine remains to be determined.

L35 ANSWER 2 OF 9 MEDLINE on STN

2004040702. PubMed ID: 14740951. Phase 1 studies of Walter Reed Army Institute of Research candidate attenuated **dengue** vaccines: selection of safe and immunogenic monovalent vaccines. Kanesa-Thasan N; Edelman R; Tacket C O; Wasserman S S; Vaughn D W; Coster T S; Kim-Ahn G J; Dubois D R; **Putnak J R**; King A; Summers P L; Innis B L; Eckels K H; Hoke C H Jr. (Walter Reed Army Institute of Research, Washington, District of Columbia, USA.. niranjan.kanesa-thasan@det.amedd.army.mil) . The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 17-23. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB We describe the results of initial safety testing of 10 live-attenuated **dengue** virus (DENV) vaccine candidates modified by serial passage in primary dog kidney (PDK) cells at the Walter Reed Army Institute of Research. The Phase 1 studies, conducted in 65 volunteers, were designed to select an attenuated vaccine candidate for each DENV serotype. No recipient of the DENV candidate vaccines sustained serious injury or required treatment. Three vaccine candidates were associated with transient idiosyncratic reactions in one volunteer each, resulting in their withdrawal from further clinical development. Increasing PDK cell passage of DENV-1, DENV-2, and DENV-3 candidate vaccines increased attenuation for volunteers, yet also decreased infectivity and immunogenicity. This effect was less clear for DENV-4 candidate vaccines following 15 and 20 PDK cell passages. Only one passage level each of the tested DENV-2, -3, and -4 vaccine candidates was judged acceptably reactogenic and suitable for expanded clinical study. Subsequent studies with more recipients will further establish safety and immunogenicity of the four selected vaccine candidates: DENV-1 45AZ5 PDK 20, DENV-2 S16803 PDK 50, DENV-3 CH53489 PDK 20, and DENV-4 341750 PDK 20.

L35 ANSWER 3 OF 9 MEDLINE on STN

2002386869. PubMed ID: 12135278. Short report: absence of protective neutralizng antibodies to West Nile virus in subjects following vaccination with Japanese encephalitis or **dengue** vaccines. Kanesa-Thasan N; **Putnak J R**; Mangiafico J A; Saluzzo J E; Ludwig G V. (Walter Reed Army Institute of Research, Washington, District of Columbia 20307-5100, USA,.. niranjan.kanesa-thasan@det.amedd.army.mil) . The American journal of tropical medicine and hygiene, (2002 Feb) Vol. 66, No. 2, pp. 115-6. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Protection of individuals against West Nile (WN) encephalitis is an emerging concern in the United States and Europe. We investigated whether immunization with licensed inactivated Japanese encephalitis (JE) vaccine or experimental live attenuated **dengue** vaccines resulted in induction of cross-neutralizing antibodies against WN virus. Protective neutralizing antibody titers to WN virus were not detected in any volunteer despite successful immunization to related flaviviruses. Vaccination against JE or **dengue** is unlikely to prevent WN virus infection but may still protect against disease.

L35 ANSWER 4 OF 9 MEDLINE on STN

2001237529. PubMed ID: 11304057. Limited potential for transmission of live **dengue** virus vaccine candidates by Aedes aegypti and Aedes albopictus. Sardelis M R; Edelman R; Klein T A; Innis B L; **Putnak J R**; Jones J W; Turell M J. (Virology Division, United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland 21702-5011, USA.) The American journal of tropical medicine and hygiene, (2000 Jun) Vol. 62, No. 6, pp. 698-701. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB To evaluate the transmission risk of four live **dengue** (DEN) vaccine candidates developed by the U.S. Army (DEN-1, 45AZ5 PDK 20; DEN-2, S16803 PDK 50; DEN-3, CH53489 PDK 20; and DEN-4, 341750 PDK 20), we tested 3,010 Aedes aegypti and 1,576 Aedes albopictus mosquitoes blood-fed on 21 volunteers who had been administered one of the four vaccine candidates or the licensed yellow fever (YF) vaccine (17D). We used an indirect immunofluorescence assay (IFA) to detect DEN or YF viral antigen in the heads of mosquitoes. Corresponding to the lack of a detectable viremia among volunteers inoculated 8-13 days previously with live DEN-1 or DEN-2 vaccine candidates, only six mosquitoes developed disseminated infections after feeding on these volunteers. These six mosquitoes included 4 of 247

Ae. albopictus fed on volunteers inoculated with the DEN-1 vaccine candidate and 2 of 528 Ae. aegypti fed on volunteers inoculated with the DEN-2 vaccine candidate. Infection was confirmed in each of these IFA-positive mosquitoes by isolating infectious virus from the mosquito's body in Vero-cell culture. None of the 1,252 or the 969 mosquitoes fed on DEN-3 or DEN-4 recipients, respectively, were infected. Overall, dissemination rates in Ae. albopictus and Ae. aegypti were low. Dissemination rates were 0.5%, 0.3%, < 0.1%, and < 0.1% for the DEN-1 through DEN-4 vaccine candidates, respectively. Because of the observed low dissemination rates, it is unlikely that these vaccine viruses would be transmitted under natural conditions.

L35 ANSWER 5 OF 9 MEDLINE on STN

2001222564. PubMed ID: 11312014. Safety and immunogenicity of attenuated **dengue** virus vaccines (Aventis Pasteur) in human volunteers. Kanesa-thasan N; Sun W; Kim-Ahn G; Van Albert S; **Putnak J R**; King A; Raengsakulsrach B; Christ-Schmidt H; Gilson K; Zahradnik J M; Vaughn D W; Innis B L; Saluzzo J F; Hoke C H Jr. (Walter Reed Army Institute of Research, Washington, DC, USA.. niranjan.kanesa-thasan@na.amedd.army.mil) . Vaccine, (2001 Apr 30) Vol. 19, No. 23-24, pp. 3179-88. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB A randomized, controlled, double-blinded study was conducted to determine safety and immunogenicity of five live attenuated **dengue** vaccines produced by Aventis Pasteur (AvP). The study was completed with 40 flavivirus non-immune volunteers: five recipients of each monovalent (**dengue**-1, **dengue**-2, **dengue**-3, or **dengue**-4) vaccine, ten recipients of tetravalent (**dengue**-1, **dengue**-2, **dengue**-3, and **dengue**-4) vaccine, and ten recipients of vaccine vehicle alone. All vaccines were administered in a single subcutaneous dose (range, 3.6-4.4 log(10) plaque forming units). No serious adverse reactions occurred in volunteers followed for 6 months after vaccination. Five vaccine recipients developed fever (T > or = 38.0 degrees C), including four tetravalent vaccinees between days 8 and 10 after vaccination. **Dengue**-1, **dengue**-2, **dengue**-3, or **dengue**-4 vaccine recipients reported similar frequency of mild symptoms of headache, malaise, and eye pain. Tetravalent vaccinees noted more moderate symptoms with onset from study days 8-11 and developed maculopapular rashes distributed over trunk and extremities. Transient neutropenia (white blood cells < 4000/mm3) was noted after vaccination but not thrombocytopenia (platelets < 100,000/mm3). All **dengue**-3, **dengue**-4, and tetravalent vaccine recipients were viremic between days 7 and 12 but viremia was rarely detected in **dengue**-1 or **dengue**-2 vaccinees. All **dengue**-2, **dengue**-3, and **dengue**-4, and 60% of **dengue**-1 vaccine recipients developed neutralizing and/or immunoglobulin M antibodies. All tetravalent vaccine recipients were viremic with **dengue**-3 virus and developed neutralizing antibodies to **dengue**-3 virus. Seven volunteers also had multivalent antibody responses, yet the highest antibody titers were against **dengue**-3 virus. The AvP live attenuated **dengue** virus vaccines are safe and tolerable in humans. The live attenuated tetravalent **dengue** vaccine was most reactogenic, and preferential replication of **dengue**-3 virus may have affected its infectivity and immunogenicity.

L35 ANSWER 6 OF 9 MEDLINE on STN

97398367. PubMed ID: 9256265. A putative cellular receptor for **dengue** viruses. **Putnak J R**; Kanesa-Thasan N; Innis B L. Nature medicine, (1997 Aug) Vol. 3, No. 8, pp. 828-9. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

L35 ANSWER 7 OF 9 MEDLINE on STN

96118136. PubMed ID: 8578812. Mice immunized with a **dengue** type 2 virus E and NS1 fusion protein made in Escherichia coli are protected against lethal **dengue** virus infection. Srivastava A K; **Putnak J R**; Warren R L; Hoke C H Jr. (Department of Virus Diseases, Walter Reed Army Institute of Research, Washington, DC 20307-5100, USA.) Vaccine, (1995 Sep) Vol. 13, No. 13, pp. 1251-8. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A gene fragment encoding the C-terminal 204 amino acids (AA) from the structural envelope glycoprotein (E) and the N-terminal 65 AA from non-structural protein one (NS1) of **dengue** type 2 virus (DEN-2) was expressed in Escherichia coli (E. coli) as a fusion protein with staphylococcal protein A. The recombinant fusion protein was purified and analysed for its antigenicity, its immunogenicity and its ability to protect mice against lethal challenge with live DEN-2 virus. The

recombinant protein was found to be reactive with anti-DEN-2 polyclonal and monoclonal antibodies. Mice immunized with the purified fusion protein made anti-DEN-2 antibodies measured by the hemagglutination-inhibition (HI) and neutralization (N) tests, and were protected against lethal challenge with DEN-2 virus administered by intracranial inoculation.

L35 ANSWER 8 OF 9 MEDLINE on STN
91029155. PubMed ID: 2224837. The **dengue** viruses. Henchal E A; **Putnak J R**. (Department of Virus Diseases, Walter Reed Army Institute of Research, Washington 20307-5100.) Clinical microbiology reviews, (1990 Oct) Vol. 3, No. 4, pp. 376-96. Ref: 298. Journal code: 8807282. ISSN: 0893-8512. Pub. country: United States. Language: English.
AB **Dengue**, a major public health problem throughout subtropical and tropical regions, is an acute infectious disease characterized by biphasic fever, headache, pain in various parts of the body, prostration, rash, lymphadenopathy, and leukopenia. In more severe or complicated **dengue**, patients present with a severe febrile illness characterized by abnormalities of hemostasis and increased vascular permeability, which in some instances results in a hypovolemic shock. Four distinct serotypes of the **dengue** virus (**dengue**-1, **dengue**-2, **dengue**-3, and **dengue**-4) exist, with numerous virus strains found worldwide. Molecular cloning methods have led to a greater understanding of the structure of the RNA genome and definition of virus-specific structural and nonstructural proteins. Progress towards producing safe, effective **dengue** virus vaccines, a goal for over 45 years, has been made.

L35 ANSWER 9 OF 9 MEDLINE on STN
88160069. PubMed ID: 2964755. Functional and antigenic domains of the **dengue**-2 virus nonstructural glycoprotein NS-1. **Putnak J R**; Charles P C; Padmanabhan R; Irie K; Hoke C H; Burke D S. (Department of Virus Diseases, Walter Reed Army Institute of Research, Washington D.C. 20307.) Virology, (1988 Mar) Vol. 163, No. 1, pp. 93-103. Journal code: 0110674. ISSN: 0042-6822. Pub. country: United States. Language: English.
AB The gene coding for the nonstructural glycoprotein of **dengue**-2 virus was cloned, sequenced, and expressed in Escherichia coli. There was about 70% conservation at the amino acid level with **dengue** serotypes 1 and 4 suggesting an important common function for this protein. Conserved hydrophobic domains were found both before the amino-terminus and at the carboxy-terminus, consistent with transmembrane roles. Evidence for at least partial translocation of NS-1 through the inner membrane of E. coli was found. Also conserved were two signals for N-linked glycosylation located near the middle of NS-1. Various regions of NS-1 were tested for antigenicity with mouse and rabbit polyclonal and mouse monoclonal antibodies. The mouse polyclonal antibodies, made against a crude **dengue**-infected mouse brain immunogen, reacted most strongly with N-terminal regions of NS-1, whereas, the rabbit antiserum, made against purified NS-1 protein, reacted strongest with C-terminal regions. These findings suggest that immunogen presentation or species differences could be important. Although most of the monoclonals appeared to be unreactive in Western blots with expressed NS-1 proteins, two appeared to react strongly; the region from amino acid (a.a.) 273 to a.a. 346 was required for antibody binding. This region, located adjacent to the two conserved C-terminal hydrophobic domains, is highly charged and contains 5 of the 10 conserved cysteine residues of NS-1.

=> d his

(FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1 3111 S DENGUE
L2 6 S L1 AND 45AZ5
L3 6 S L2 AND PDK-27
L4 14 S L1 AND S16803
L5 9 S L4 NOT L2
L6 1 S L5 AND PDK-50
L7 12 S L1 AND CH53489
L8 7 S L7 NOT (L3 OR L6)
L9 0 S L8 AND PDK-20
L10 9 S L1 AND 341750
L11 4 S L10 NOT (L3 OR L6)
L12 95 S L1 AND TETRAVALENT
L13 2 S L12 AND TETRAVALENT/CLM

```
L14           1 S L13 NOT (L3 OR L5 OR L8)

     FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006
L15         551 S DENGUE
L16           2 S L15 AND 45AZ5
L17           2 S L15 AND S16803
L18           0 S L17 NOT L16
L19           1 S L15 AND CH53489
L20           1 S L19 NOT L16
L21           4 S L15 AND 341750
L22           2 S L21 NOT (L16 OR L17 OR L19)
L23           6 S L15 AND TETRAVALENT
L24           6 S L23 NOT (L16 OR L17 OR L19)

     FILE 'MEDLINE' ENTERED AT 13:05:50 ON 29 DEC 2006
L25        5433 S DENGUE
L26         197 S L25 AND ATTENUATE?
L27          19 S L26 AND (SERIAL PASSAGE?)
L28           5 S L27 AND (PRIMARY KIDNEY CELLS)
L29          12 S L27 AND (PRIMARY DOG KIDNEY)
L30           7 S L29 NOT L28
                E ECKELS K/AU
L31           8 S E5
L32           7 S L31 AND DENGUE
                E PUTNAK J R/AU
L33          21 S E3-E4
L34          11 S L33 AND DENGUE
L35           9 S L34 NOT L31

=> e dubois d r/au
E1           10      DUBOIS D M/AU
E2            1      DUBOIS D P/AU
E3           31 --> DUBOIS D R/AU
E4            2      DUBOIS D W/AU
E5           15      DUBOIS D Y/AU
E6          102      DUBOIS DALCQ M/AU
E7            9      DUBOIS DALCQ M E/AU
E8            8      DUBOIS DALCQ MONIQUE/AU
E9            1      DUBOIS DALE/AU
E10           1      DUBOIS DALQ M/AU
E11           3      DUBOIS DAMIEN/AU
E12           1      DUBOIS DAN/AU

=> e dubois doria r/au
E1            2      DUBOIS DIDIER/AU
E2           15      DUBOIS DOMINIQUE/AU
E3            1 --> DUBOIS DORIA R/AU
E4            4      DUBOIS DUSTIN W/AU
E5           85      DUBOIS E/AU
E6           17      DUBOIS E A/AU
E7            1      DUBOIS E C/AU
E8           10      DUBOIS E F/AU
E9            4      DUBOIS E F L/AU
E10           1      DUBOIS E G/AU
E11           1      DUBOIS E I/AU
E12           1      DUBOIS E JEAN/AU

=> s e3
L36           1 "DUBOIS DORIA R"/AU

=> d 136,cbib,ab

L36  ANSWER 1 OF 1     MEDLINE on STN
2004040701.     PubMed ID: 14740950.   Modification of dengue virus strains by
     passage in primary dog kidney cells: preparation of candidate vaccines and
     immunization of monkeys. Eckels Kenneth H; Dubois Doria R; Putnak
     Robert; Vaughn David W; Innis Bruce L; Henchal Erik A; Hoke Charles H Jr.
     (Division of Communicable Diseases and Immunology, Walter Reed Army
     Institute of Research, Silver Spring, Maryland 20910, USA. ) The American
     journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl,
     pp. 12-6.  Journal code: 0370507. ISSN: 0002-9637. Pub. country: United
     States. Language: English.
AB   Dengue (DENV) virus strains for each of the four DENV serotypes were
     modified by passage in primary dog kidney (PDK) cell cultures with final
     manufacture of vaccine lots in fetal rhesus monkey diploid cell cultures.
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"Strain sets" consisting of serially-passaged DENV were inoculated in rhesus monkeys along with unmodified parent viruses for each strain. Vaccine candidates were compared with unmodified parent viruses by measuring viremia and immune responses. All except one DENV-1 strain demonstrated reduced infection in monkeys after PDK cell passage. A DENV-3 strain lost all monkey infectivity after PDK cell passage. Twelve vaccine candidates were selected for Phase 1 human trials through this selection process.

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=> e innis b l/au
E1            1      INNIS A/AU
E2            7      INNIS B/AU
E3           80 --> INNIS B L/AU
E4            1      INNIS B T/AU
E5            1      INNIS BRUCE/AU
E6           21      INNIS BRUCE L/AU
E7            1      INNIS C/AU
E8            7      INNIS C A/AU
E9            2      INNIS C AXEL/AU
E10           3      INNIS C O/AU
E11           1      INNIS CHARLES J/AU
E12           1      INNIS D P/AU

=> s e5-e6
              1 "INNIS BRUCE"/AU
             21 "INNIS BRUCE L"/AU
L37          22 ("INNIS BRUCE"/AU OR "INNIS BRUCE L"/AU)

=> s l37 and dengue
           5433 DENGUE
L38          10 L37 AND DENGUE

=> s l38 and attenuate?
          96308 ATTENUATE?
L39           7 L38 AND ATTENUATE?

=> d his

     (FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

     FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1          3111 S DENGUE
L2             6 S L1 AND 45AZ5
L3             6 S L2 AND PDK-27
L4            14 S L1 AND S16803
L5             9 S L4 NOT L2
L6             1 S L5 AND PDK-50
L7            12 S L1 AND CH53489
L8             7 S L7 NOT (L3 OR L6)
L9             0 S L8 AND PDK-20
L10            9 S L1 AND 341750
L11            4 S L10 NOT (L3 OR L6)
L12           95 S L1 AND TETRAVALENT
L13            2 S L12 AND TETRAVALENT/CLM
L14            1 S L13 NOT (L3 OR L5 OR L8)

     FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006
L15          551 S DENGUE
L16            2 S L15 AND 45AZ5
L17            2 S L15 AND S16803
L18            0 S L17 NOT L16
L19            1 S L15 AND CH53489
L20            1 S L19 NOT L16
L21            4 S L15 AND 341750
L22            2 S L21 NOT (L16 OR L17 OR L19)
L23            6 S L15 AND TETRAVALENT
L24            6 S L23 NOT (L16 OR L17 OR L19)

     FILE 'MEDLINE' ENTERED AT 13:05:50 ON 29 DEC 2006
L25         5433 S DENGUE
L26          197 S L25 AND ATTENUATE?
L27           19 S L26 AND (SERIAL PASSAGE?)
L28            5 S L27 AND (PRIMARY KIDNEY CELLS)
L29           12 S L27 AND (PRIMARY DOG KIDNEY)
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L30             7 S L29 NOT L28
                E ECKELS K/AU
L31             8 S E5
L32             7 S L31 AND DENGUE
                E PUTNAK J R/AU
L33            21 S E3-E4
L34            11 S L33 AND DENGUE
L35             9 S L34 NOT L31
                E DUBOIS D R/AU
                E DUBOIS DORIA R/AU
L36             1 S E3
                E INNIS B L/AU
L37            22 S E5-E6
L38            10 S L37 AND DENGUE
L39             7 S L38 AND ATTENUATE?

=> s l39 not (l31 or l33 or l36)
L40             1 L39 NOT (L31 OR L33 OR L36)

=> d l40,cbib,ab

L40  ANSWER 1 OF 1      MEDLINE on STN
2004040705.     PubMed ID: 14740954.   Serotype-specific T(H)1 responses in
     recipients of two doses of candidate live-attenuated dengue virus
     vaccines. Gwinn William; Sun Wellington; Innis Bruce L; Caudill Jeffrey;
     King Alan D. (Department of Virus Diseases, Walter Reed Army Institute of
     Research, Silver Spring, Maryland 20910, USA. ) The American journal of
     tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 39-47.
     Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States.
     Language: English.
AB   As part of a larger vaccine study, peripheral blood mononuclear cells
     (PBMC) were collected from volunteers for analysis of vaccine-induced T
     cell responses.  The PBMC were re-stimulated in vitro with live dengue
     virus and assayed for T(H)1 or T(H)2 memory cell responses.  Re-stimulated
     PBMC from the volunteers predominantly secreted interferon-gamma.  Little
     interleukin-4 (IL-4) or IL-10 secretion was detected, indicating a T(H)1
     type of T cell response.  The interferon-gamma response was primarily
     serotype-specific with some serotype cross-reactivity.  T cell depletion
     studies showed that the interferon-gamma was being secreted by CD4+ T
     lymphocytes and/or by cells other than CD8+ T lymphocytes that were being
     stimulated by the CD4+ T lymphocytes.  CD3+ or CD8+ T cell depletion
     showed that granzyme B mRNA expression correlated with the presence of
     CD4+ T lymphocytes.  However, depletion of CD4+ T cells after four days of
     stimulation indicated that the granzyme B mRNA was produced by cells in
     culture other than lymphocytes.  In summary, an antigen-specific T(H)1
     type T cell response was seen as a response to vaccination using live
     attenuated dengue virus.


=> e hoke c h/au
E1              1      HOKE B H/AU
E2             18      HOKE C/AU
E3             25 --> HOKE C H/AU
E4             36      HOKE C H JR/AU
E5              2      HOKE C JR/AU
E6              1      HOKE CASSANDRA N/AU
E7              1      HOKE CHARLES D/AU
E8              1      HOKE CHARLES H/AU
E9              3      HOKE CHARLES H JR/AU
E10             6      HOKE D/AU
E11             2      HOKE D E/AU
E12             1      HOKE DAVID/AU

=> s e2-e5
            18 "HOKE C"/AU
            25 "HOKE C H"/AU
            36 "HOKE C H JR"/AU
             2 "HOKE C JR"/AU
L41         81 ("HOKE C"/AU OR "HOKE C H"/AU OR "HOKE C H JR"/AU OR "HOKE C
               JR"/AU)

=> s l41 and dengue
          5433 DENGUE
L42         25 L41 AND DENGUE
```

```
=> s l42 and attenuate?
         96308 ATTENUATE?
L43          12 L42 AND ATTENUATE?

=> d his

     (FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

     FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006
L1         3111 S DENGUE
L2            6 S L1 AND 45AZ5
L3            6 S L2 AND PDK-27
L4           14 S L1 AND S16803
L5            9 S L4 NOT L2
L6            1 S L5 AND PDK-50
L7           12 S L1 AND CH53489
L8            7 S L7 NOT (L3 OR L6)
L9            0 S L8 AND PDK-20
L10           9 S L1 AND 341750
L11           4 S L10 NOT (L3 OR L6)
L12          95 S L1 AND TETRAVALENT
L13           2 S L12 AND TETRAVALENT/CLM
L14           1 S L13 NOT (L3 OR L5 OR L8)

     FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006
L15         551 S DENGUE
L16           2 S L15 AND 45AZ5
L17           2 S L15 AND S16803
L18           0 S L17 NOT L16
L19           1 S L15 AND CH53489
L20           1 S L19 NOT L16
L21           4 S L15 AND 341750
L22           2 S L21 NOT (L16 OR L17 OR L19)
L23           6 S L15 AND TETRAVALENT
L24           6 S L23 NOT (L16 OR L17 OR L19)

     FILE 'MEDLINE' ENTERED AT 13:05:50 ON 29 DEC 2006
L25        5433 S DENGUE
L26         197 S L25 AND ATTENUATE?
L27          19 S L26 AND (SERIAL PASSAGE?)
L28           5 S L27 AND (PRIMARY KIDNEY CELLS)
L29          12 S L27 AND (PRIMARY DOG KIDNEY)
L30           7 S L29 NOT L28
                E ECKELS K/AU
L31           8 S E5
L32           7 S L31 AND DENGUE
                E PUTNAK J R/AU
L33          21 S E3-E4
L34          11 S L33 AND DENGUE
L35           9 S L34 NOT L31
                E DUBOIS D R/AU
                E DUBOIS DORIA R/AU
L36           1 S E3
                E INNIS B L/AU
L37          22 S E5-E6
L38          10 S L37 AND DENGUE
L39           7 S L38 AND ATTENUATE?
L40           1 S L39 NOT (L31 OR L33 OR L36)
                E HOKE C H/AU
L41          81 S E2-E5
L42          25 S L41 AND DENGUE
L43          12 S L42 AND ATTENUATE?

=> s l43 not (l31 or l33 or l36 or l37)
L44          10 L43 NOT (L31 OR L33 OR L36 OR L37)

=> d l44,cbib,ab,1-10

L44  ANSWER 1 OF 10      MEDLINE on STN
1998030041.     PubMed ID: 9363590.    T cell activation in vivo by dengue
     virus infection. Kurane I; Innis B L; Hoke C H Jr; Eckels K H; Meager A;
     Janus J; Ennis F A. (Department of Medicine, University of Massachusetts
     Medical Center, Worcester 01655, USA. ) Journal of clinical & laboratory
     immunology, (1995) Vol. 46, No. 1, pp. 35-40.  Journal code: 7808987.
     ISSN: 0141-2760. Pub. country: SCOTLAND: United Kingdom. Language:
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English.

AB It is accepted that T cells play a critical role during virus infections; however, T cell responses in vivo in acute stage of virus infection are not understood. We examined T cell activation in vivo in two volunteers who developed **dengue** fever in response to vaccination with a candidate live **dengue** vaccine. Serial plasma collected from the volunteers from day 0 (before infection) to day 17 after infection were examined for levels of soluble interleukin-2 receptor (sIL-2R), soluble CD4 (sCD4), soluble CD8 (sCD8), interleukin-2 (IL-2) and interferon gamma (INF gamma). Elevation of the levels of sIL-2R, IFN gamma, sCD4 and IL-2 became obvious during the period of viremia and was followed by a later increase in the level of sCD8. The levels of IFN gamma and sIL-2R declined after the end of the period of viremia. These results indicate that i. T cells are activated in vivo by **dengue** virus infection ii. activation of CD4+ T cells occurs during the period of viremia iii. activation of CD8+ T cells follows CD4+ T cell activation. These results suggest that activation of T cells in vivo may contribute to controlling acute **dengue** virus infections.

L44 ANSWER 2 OF 10 MEDLINE on STN

97437483. PubMed ID: 9292016. Molecular analysis of **dengue** virus attenuation after serial passage in primary dog kidney cells. Puri B; Nelson W M; Henchal E A; **Hoke C H**; Eckels K H; Dubois D R; Porter K R; Hayes C G. (Infectious Diseases Department, Naval Medical Research Institute, Bethesda, Maryland 20889-5607, USA.. PURI@MAIL2.NMRI.NNMC.NAVY.MIL) . The Journal of general virology, (1997 Sep) Vol. 78 (Pt 9), pp. 2287-91. Journal code: 0077340. ISSN: 0022-1317. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The complete nucleotide sequences of the genomes of **dengue**-1 virus virulent 45AZ5 PDK-O and **attenuated** vaccine candidate strain 45AZ5 PDK-27 have been determined and compared with the **dengue**-1 virus Western Pacific (West Pac) 74 parent strain from which 45AZ5 PDK-O was derived. Twenty-five (0.23%) nucleotide and 10 (0.29%) amino acid substitutions occurred between parent strain **dengue**-1 virus West Pac 74 and virulent strain 45AZ5 PDK-O, which was derived from the parent by serial passage in diploid foetal rhesus lung (FRhL-2) and mutagenized with 5-azacytidine. These substitutions were preserved in the 45AZ5 PDK-27 vaccine. 45AZ5 PDK-O and PDK-27 strains, which differ by 27 passages in primary dog kidney (PDK) cells, show 25 (0.23%) nucleotide and 11 (0.32%) amino acid divergences. These comparative studies suggest that the changes which occurred between the West Pac 74 and 45AZ5 PDK-O strains may alter the biological properties of the virus but may not be important for attenuation. Important nucleotide base changes responsible for attenuation accumulated between 45AZ5 PDK-O and 27.

L44 ANSWER 3 OF 10 MEDLINE on STN

96300644. PubMed ID: 8744561. Testing of a **dengue** 2 live-**attenuated** vaccine (strain 16681 PDK 53) in ten American volunteers. Vaughn D W; **Hoke C H Jr**; Yoksan S; LaChance R; Innis B L; Rice R M; Bhamarapravati N. (Armed Forces Research Institute of Medical Sciences, APO AP 96546, USA.) Vaccine, (1996 Mar) Vol. 14, No. 4, pp. 329-36. Journal code: 8406899. ISSN: 0264-410X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A live-**attenuated dengue** 2 vaccine (strain 16681 PDK 53) developed at Mahidol University, Thailand was evaluated for safety and immunogenicity by administering 10(4) p.f.u. subcutaneously to ten flavivirus non-immune American volunteers. The vaccine was safe; there were no serious adverse reactions. Eight recipients experienced no or mild side effects. One recipient reported headaches on 7 separate days. One volunteer, who had a fracture of the humerus 1 day after vaccination requiring surgical repair, experienced generalized malaise with fever (maximum temperature = 38.9 degrees C), headache, eye pain and myalgia lasting less than 24 h. The vaccine was highly immunogenic; all recipients developed neutralizing antibody that persisted for two years.

L44 ANSWER 4 OF 10 MEDLINE on STN

95201101. PubMed ID: 7893886. Quantitative relationship between oral temperature and severity of illness following inoculation with candidate **attenuated dengue** virus vaccines. Mackowiak P A; Wasserman S S; Tacket C O; Vaughn D W; Eckels K H; Dubois D R; **Hoke C H**; Edelman R. (Department of Veterans Affairs Medical Center, Baltimore, Maryland 21201.) Clinical infectious diseases : an official publication of the Infectious Diseases Society of America, (1994 Nov) Vol. 19, No. 5, pp. 948-50. Journal code: 9203213. ISSN: 1058-4838. Pub. country: United States. Language: English.

AB The relationship between oral temperature and other parameters of illness was examined in 51 adult volunteers who were inoculated experimentally with partially **attenuated** candidate **dengue** virus vaccines. In subjects who developed clinical illness, the peak illness temperature, mean illness temperature, and peak 6:00 A.M. illness temperature all correlated positively with the total number of signs and symptoms other than fever and with a fall in the white blood cell count (the latter was the only laboratory abnormality significantly associated with clinical illness [P = .02]). Of these factors, the peak 6:00 A.M. oral temperature exhibited the strongest correlations with the two parameters used to estimate severity of illness (rxy = .58 and P < .01 for signs and symptoms; rxy = .37 and P = .01 for fall in white blood cell count).

L44 ANSWER 5 OF 10 MEDLINE on STN

95088425. PubMed ID: 7995984. A live **attenuated dengue**-1 vaccine candidate (45AZ5) passaged in primary dog kidney cell culture is **attenuated** and immunogenic for humans. Edelman R; Tacket C O; Wasserman S S; Vaughn D W; Eckels K H; Dubois D R; Summers P L; **Hoke C H**. (Department of Medicine, University of Maryland School of Medicine, Baltimore 21201.) The Journal of infectious diseases, (1994 Dec) Vol. 170, No. 6, pp. 1448-55. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB A **dengue**-1 candidate vaccine (45AZ5), previously found to be underattenuated in 2 volunteers, was further **attenuated** by passage in primary dog kidney (PDK) cell cultures. New candidate vaccines prepared from three levels of PDK-passaged virus, PDK-10, PDK-20, and PDK-27, were each injected into 9 or 10 volunteers. There was a significant, progressive decline in viremia, clinical illness, and hematologic changes from low to high PDK cell passage level. PDK-20 infected all 10 vaccinees and induced viremia in 5, transient fever in 3, symptoms that resulted in curtailed activities for < or = 1 day in 4, and neutralizing antibody in all 10, which persisted for > or = 1 year in 5 of 8 vaccinees tested. Progressive passage in PDK cell culture progressively **attenuates** vaccine candidate strain 45AZ5 for humans. Because passage level PDK-20 may be suitable for healthy adults at high risk of **dengue** fever, additional clinical trials of this strain are warranted.

L44 ANSWER 6 OF 10 MEDLINE on STN

94284658. PubMed ID: 7912253. **Dengue** virus-specific memory T cell responses in human volunteers receiving a live **attenuated dengue** virus type 2 candidate vaccine. Dharakul T; Kurane I; Bhamarapravati N; Yoksan S; Vaughn D W; **Hoke C H**; Ennis F A. (Department of Microbiology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand.) The Journal of infectious diseases, (1994 Jul) Vol. 170, No. 1, pp. 27-33. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB A live **attenuated dengue** virus type 2 candidate vaccine (16681-PDK53) was evaluated in a phase I trial in 10 nonimmune adult volunteers. The **dengue** virus-specific memory T cell responses were analyzed as part of this study. **Dengue** virus-specific T cell proliferative responses were observed in all subjects after stimulating their peripheral blood mononuclear cells with live viruses or noninfectious viral antigens. The highest proliferative response was against **dengue** virus type 2, although cross-reactivity with other flaviviruses was detected to a lesser degree in some subjects. **Dengue** virus type 2-specific CD4+ and CD8+ cytotoxic T lymphocytes were generated in all vaccinees. This study investigated whether the candidate vaccine was efficacious in inducing **dengue** virus-specific CD4+ and CD8+ T cell memory after a single immunization in nonimmune recipients.

L44 ANSWER 7 OF 10 MEDLINE on STN

93381798. PubMed ID: 8371350. **Dengue** virus-specific human CD4+ T-lymphocyte responses in a recipient of an experimental live-**attenuated dengue** virus type 1 vaccine: bulk culture proliferation, clonal analysis, and precursor frequency determination. Green S; Kurane I; Edelman R; Tacket C O; Eckels K H; Vaughn D W; **Hoke C H Jr**; Ennis F A. (Department of Medicine, University of Massachusetts Medical Center, Worcester 01655.) Journal of virology, (1993 Oct) Vol. 67, No. 10, pp. 5962-7. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB We analyzed the CD4+ T-lymphocyte responses to **dengue**, West Nile, and yellow fever viruses 4 months after immunization of a volunteer with an experimental live-**attenuated dengue** virus type 1 vaccine (DEN-1 45AZ5). We examined bulk culture proliferation to noninfectious antigens, determined the precursor frequency of specific CD4+ T cells by limiting

dilution, and established and analyzed CD4+ T-cell clones. Bulk culture proliferation was predominantly **dengue** virus type 1 specific with a lesser degree of cross-reactive responses to other **dengue** virus serotypes, West Nile virus, and yellow fever virus. Precursor frequency determination by limiting dilution in the presence of noninfectious **dengue** virus antigens revealed a frequency of antigen-reactive cells of 1 in 1,686 peripheral blood mononuclear cells (PBMC) for **dengue** virus type 1, 1 in 9,870 PBMC for **dengue** virus type 3, 1 in 14,053 PBMC for **dengue** virus type 2, and 1 in 17,690 PBMC for **dengue** virus type 4. Seventeen CD4+ T-cell clones were then established by using infectious **dengue** virus type 1 as antigen. Two patterns of **dengue** virus specificity were found in these clones. Thirteen clones were **dengue** virus type 1 specific, and four clones recognized both **dengue** virus types 1 and 3. Analysis of human leukocyte antigen (HLA) restriction revealed that five clones are HLA-DRw52 restricted, one clone is HLA-DP3 restricted, and one clone is HLA-DP4 restricted. These results indicate that in this individual, the CD4+ T-lymphocyte responses to immunization with live-**attenuated** **dengue** virus type 1 vaccine are predominantly serotype specific and suggest that a multivalent vaccine may be necessary to elicit strong serotype-cross-reactive CD4+ T-lymphocyte responses in such individuals.

L44 ANSWER 8 OF 10 MEDLINE on STN

90358303. PubMed ID: 2389825. Preparation of an **attenuated** **dengue** 4 (341750 Carib) virus vaccine. II. Safety and immunogenicity in humans. **Hoke C H Jr**; Malinoski F J; Eckels K H; Scott R M; Dubois D R; Summers P L; Simms T; Burrous J; Hasty S E; Bancroft W H. (Walter Reed Army Institute of Research, Washington, DC.) The American journal of tropical medicine and hygiene, (1990 Aug) Vol. 43, No. 2, pp. 219-26. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB To determine safety and immunogenicity, a single 0.5-ml dose of a monovalent live-**attenuated** **dengue** (DEN) 4 (341750 Carib) vaccine was given sc to 3 groups of flavivirus nonimmune volunteers in increasing concentrations. Two recipients received 10(3) plaque forming units (PFU)/dose (1:100 dilution of stock vaccine). One remained asymptomatic, but became viremic between days 12 and 15, experienced a mild elevation of temperature (37.4 degrees C), and developed DEN-4 specific antibody. Neither recipient of the 10(4) PFU became infected. Eight volunteers then received undiluted vaccine (10(5) PFU). Viremia and antibody (neutralizing, hemagglutination inhibition, and IgM) developed in 5 of the 8 (63%). These 5 volunteers also developed a scarcely noticeable macular, blanching rash and minimal temperature elevations (37.3, 38.1, 37, 37.9, and 37.9 degrees C). Clinically insignificant decreases in total white blood cell, lymphocyte, and polymorphonuclear cell counts and an elevation in mononuclear cell counts occurred in association with viremia. This vaccine is safe, reasonably immunogenic, and suitable for further evaluation.

L44 ANSWER 9 OF 10 MEDLINE on STN

88318809. PubMed ID: 2842677. Protection against Japanese encephalitis by inactivated vaccines. **Hoke C H**; Nisalak A; Sangawhipa N; Jatanasen S; Laorakapongse T; Innis B L; Kotchasenee S; Gingrich J B; Latendresse J; Fukai K; +. (U.S. Army Medical Component, Armed Forces Research Institute of Medical Sciences, Bangkok, Thailand.) The New England journal of medicine, (1988 Sep 8) Vol. 319, No. 10, pp. 608-14. Journal code: 0255562. ISSN: 0028-4793. Pub. country: United States. Language: English.

AB Encephalitis caused by Japanese encephalitis virus occurs in annual epidemics throughout Asia, making it the principal cause of epidemic viral encephalitis in the world. No currently available vaccine has demonstrated efficacy in preventing this disease in a controlled trial. We performed a placebo-controlled, blinded, randomized trial in a northern Thai province, with two doses of monovalent (Nakayama strain) or bivalent (Nakayama plus Beijing strains) inactivated, purified Japanese encephalitis vaccine made from whole virus derived from mouse brain. We examined the effect of these vaccines on the incidence and severity of Japanese encephalitis and **dengue** hemorrhagic fever, a disease caused by a closely related flavivirus. Between November 1984 and March 1985, 65,224 children received two doses of monovalent Japanese encephalitis vaccine (n = 21,628), bivalent Japanese encephalitis vaccine (n = 22,080), or tetanus toxoid placebo (n = 21,516), with only minor side effects. The cumulative attack rate for encephalitis due to Japanese encephalitis virus was 51 per 100,000 in the placebo group and 5 per 100,000 in each vaccine group. The efficacy in both vaccine groups combined was 91 percent (95 percent confidence interval, 70 to 97 percent). Attack rates for **dengue**

hemorrhagic fever declined, but not significantly. The severity of cases of **dengue** was also reduced. We conclude that two doses of inactivated Japanese encephalitis vaccine, either monovalent or bivalent, protect against encephalitis due to Japanese encephalitis virus and may have a limited beneficial effect on the severity of **dengue** hemorrhagic fever.

L44 ANSWER 10 OF 10 MEDLINE on STN
84241242. PubMed ID: 6376649. **Dengue** virus type 2 vaccine: reactogenicity and immunogenicity in soldiers. Bancroft W H; Scott R M; Eckels K H; **Hoke C H Jr**; Simms T E; Jesrani K D; Summers P L; Dubois D R; Tsoulos D; Russell P K. The Journal of infectious diseases, (1984 Jun) Vol. 149, No. 6, pp. 1005-10. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.
AB A live **dengue** virus type 2 (**dengue**-2) vaccine (PR-159/S-1) was tested for reactogenicity and immunogenicity in a placebo-controlled, double-blind clinical trial involving 98 soldiers. Seroconversion rates based on the development of neutralizing antibody to **dengue**-2 were 90% in 70 recipients with immunity to yellow fever and 61% in 28 vaccinees without such immunity (P less than .01). Peak titers of neutralizing antibody were three times higher in recipients with antibody to yellow fever virus and persisted in most for at least 18 months. Individuals seroconverting to the vaccine virus more frequently experienced systemic symptoms than those who received placebo (P less than .02). Future users of this **dengue**-2 vaccine may wish to employ immunization schedules that include preliminary immunization against yellow fever and must be prepared to accept mild vaccine-related symptoms in some recipients.

```
=> e sun w/au
E1            1     SUN VIRGINIA/AU
E2            1     SUN VIRGINIA C/AU
E3          313 --> SUN W/AU
E4            5     SUN W B/AU
E5            3     SUN W C/AU
E6            7     SUN W D/AU
E7           14     SUN W F/AU
E8            9     SUN W G/AU
E9           34     SUN W H/AU
E10          25     SUN W J/AU
E11           8     SUN W K/AU
E12          13     SUN W L/AU

=> s e3
L45         313 "SUN W"/AU

=> s l45 and dengue
          5433 DENGUE
L46          7 L45 AND DENGUE

=> s l46 and attenuat?
        123198 ATTENUAT?
L47          4 L46 AND ATTENUAT?

=> d l47,cbbi,ab,1-4
'CBBI' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, AU, CS, NC, SO, CM, CY, DT, LA, FS, OS, EM,
         ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, ST, CT, NA, RN, CN, GEN
TRI ---- TI, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
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KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and PY.

To display a particular field or fields, enter the display field codes. For a list of display field codes, enter 'HELP DFIELDS' at an arrow prompt (=>). Examples of formats include: 'BIB'; 'AB'; 'SO,ST'. You may specify the format fields in any order, and the information will be displayed in the same order as the format specification.

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ENTER DISPLAY FORMAT (BIB):d 147,cbib,ab,1-4
'D' IS NOT A VALID FORMAT FOR FILE 'MEDLINE'

The following are valid formats:

The default display format is BIB.

ABS ---- AB
ALL ---- AN, DN, TI, AU, CS, NC, SO, CM, CY, DT, LA, FS, OS, EM, ED, AB, ST, CT, NA, RN, CN, GEN
BIB ---- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
CBIB --- AN, DN, TI, AU, CS, NC, SO, CY, DT, LA, FS, OS, EM, ED
DALL --- ALL, delimited for post processing
IABS --- ABS, with a text label
IALL --- ALL, indented with text labels
IBIB --- BIB, indented with text labels
IND ---- ST, CT, NA, RN, CN, GEN
SAM ---- TI, ST, CT, NA, RN, CN, GEN
TRI ---- TI, ST, CT, NA, RN, CN, GEN
TRIAL -- TI, ST, CT, NA, RN, CN, GEN
HIT ---- All fields containing hit terms
HITIND - IND
KWIC --- All hit terms plus 20 words on either side
OCC ---- List of display fields containing hit terms

Hit terms will be highlighted in all available fields except CM and PY.

To display a particular field or fields, enter the display field codes. For a list of display field codes, enter 'HELP DFIELDS' at an arrow prompt (=>). Examples of formats include: 'BIB'; 'AB'; 'SO,ST'. You may specify the format fields in any order, and the information will be displayed in the same order as the format specification.

The same formats (except for HIT, HITIND, KWIC, and OCC) may be used with the DISPLAY ACC command to display the record for a specified Accession Number.
ENTER DISPLAY FORMAT (BIB):cbib,ab

L47 ANSWER 1 OF 4 MEDLINE on STN
2004040704. PubMed ID: 14740953. Atypical antibody responses in **dengue** vaccine recipients. Kanesa-Thasan N; **Sun W**; Ludwig G V; Rossi C; Putnak J R; Mangiafico J A; Innis B L; Edelman R. (Walter Reed Army Institute of Research, Washington, District of Columbia, USA.. niranjan.kanesa-thasan@det.amedd.army.mil) . The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 32-8. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.
AB Eight of 69 (12%) healthy adult volunteers vaccinated with monovalent live-**attenuated dengue** virus (DENV) vaccine candidates had atypical antibody responses, with depressed IgM:IgG antibody ratios and induction of high-titer hemagglutination-inhibiting and neutralizing (NT) antibodies to all four DENV serotypes. These features suggested flavivirus exposure prior to DENV vaccination, yet no volunteer had a history of previous flavivirus infection, flavivirus vaccination, or antibody to flaviviruses evident before DENV vaccination. Moreover, production of antibody to DENV by atypical responders (AR) was not accelerated compared with antibody responses in the 61 flavivirus-naive responders (NR). Further evaluation revealed no differences in sex, age, race, DENV vaccine candidate

received, or clinical signs and symptoms following vaccination between AR and NR. However, viremia was delayed at the onset in AR compared with NR. A comparative panel of all AR and five randomly selected NR found flavivirus cross-reactive antibody after vaccination only in AR. Unexpectedly, six of eight AR had NT antibodies to yellow fever virus (YFV) > 1:10 before vaccination while NR had none (P = 0.04). The AR also universally demonstrated YFV NT antibody titers > or = 1:160 after DENV vaccination, whereas four of five NR failed to seroconvert (P = 0.02). Yellow fever virus priming broadens the antibody response to monovalent DENV vaccination. The effect of flavivirus priming on the clinical and immunologic response to tetravalent DENV vaccine remains to be determined.

L47 ANSWER 2 OF 4 MEDLINE on STN

2001670724. PubMed ID: 11716091. **Attenuation** and immunogenicity in humans of a live **dengue** virus type-4 vaccine candidate with a 30 nucleotide deletion in its 3'-untranslated region. Durbin A P; Karron R A; **Sun W**; Vaughn D W; Reynolds M J; Perreault J R; Thumar B; Men R; Lai C J; Elkins W R; Chanock R M; Murphy B R; Whitehead S S. (Center for Immunization Research, Johns Hopkins School of Public Health, Baltimore, Maryland 21205, USA.) The American journal of tropical medicine and hygiene, (2001 Nov) Vol. 65, No. 5, pp. 405-13. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB The recombinant **dengue** virus type-4 vaccine candidate 2AA30 was **attenuated** in rhesus monkeys due to an engineered 30-nucleotide deletion in the 3'-untranslated region of the viral genome. A clinical trial to evaluate the safety and immunogenicity of a single dose of 2Adelta30 was conducted with 20 adult human volunteers. The vaccine candidate was well tolerated and did not cause systemic illness in any of the 20 volunteers. Viremia was detectable in 14 volunteers at a mean level of 1.6 log10 plaque-forming units/ml of serum, although all 20 volunteers seroconverted with a seven-fold or greater increase in serum neutralizing antibody titer on day 28 post-vaccination (mean titer = 1:580). A mild, asymptomatic, macular rash developed in 10 volunteers, and a transient elevation in the serum level of alanine aminotransferase was noted in five volunteers. The low level of reactogenicity and high degree of immunogenicity of this vaccine candidate warrant its further evaluation and its use to create chimeric vaccine viruses expressing the structural genes of **dengue** virus types 1, 2, and 3.

L47 ANSWER 3 OF 4 MEDLINE on STN

2001222564. PubMed ID: 11312014. Safety and immunogenicity of **attenuated dengue** virus vaccines (Aventis Pasteur) in human volunteers. Kanesa-thasan N; **Sun W**; Kim-Ahn G; Van Albert S; Putnak J R; King A; Raengsakulsrach B; Christ-Schmidt H; Gilson K; Zahradnik J M; Vaughn D W; Innis B L; Saluzzo J F; Hoke C H Jr. (Walter Reed Army Institute of Research, Washington, DC, USA.. niranjan.kanesa-thasan@na.amedd.army.mil) . Vaccine, (2001 Apr 30) Vol. 19, No. 23-24, pp. 3179-88. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB A randomized, controlled, double-blinded study was conducted to determine safety and immunogenicity of five live **attenuated dengue** vaccines produced by Aventis Pasteur (AvP). The study was completed with 40 flavivirus non-immune volunteers: five recipients of each monovalent (**dengue**-1, **dengue**-2, **dengue**-3, or **dengue**-4) vaccine, ten recipients of tetravalent (**dengue**-1, **dengue**-2, **dengue**-3, and **dengue**-4) vaccine, and ten recipients of vaccine vehicle alone. All vaccines were administered in a single subcutaneous dose (range, 3.6-4.4 log(10) plaque forming units). No serious adverse reactions occurred in volunteers followed for 6 months after vaccination. Five vaccine recipients developed fever (T > or = 38.0 degrees C), including four tetravalent vaccinees between days 8 and 10 after vaccination. **Dengue**-1, **dengue**-2, **dengue**-3, or **dengue**-4 vaccine recipients reported similar frequency of mild symptoms of headache, malaise, and eye pain. Tetravalent vaccinees noted more moderate symptoms with onset from study days 8-11 and developed maculopapular rashes distributed over trunk and extremities. Transient neutropenia (white blood cells < 4000/mm3) was noted after vaccination but not thrombocytopenia (platelets < 100,000/mm3). All **dengue**-3, **dengue**-4, and tetravalent vaccine recipients were viremic between days 7 and 12 but viremia was rarely detected in **dengue**-1 or **dengue**-2 vaccinees. All **dengue**-2, **dengue**-3, and **dengue**-4, and 60% of **dengue**-1 vaccine recipients developed neutralizing and/or immunoglobulin M antibodies. All tetravalent vaccine recipients were viremic with **dengue**-3 virus and developed neutralizing antibodies to **dengue**-3 virus. Seven volunteers also had multivalent antibody responses, yet the highest antibody titers

were against **dengue**-3 virus. The AvP live **attenuated dengue** virus vaccines are safe and tolerable in humans. The live **attenuated** tetravalent **dengue** vaccine was most reactogenic, and preferential replication of **dengue**-3 virus may have affected its infectivity and immunogenicity.

L47 ANSWER 4 OF 4 MEDLINE on STN
2000348035. PubMed ID: 10888933. Human skin Langerhans cells are targets of **dengue** virus infection. Wu S J; Grouard-Vogel G; **Sun W**; Mascola J R; Brachtel E; Putvatana R; Louder M K; Filgueira L; Marovich M A; Wong H K; Blauvelt A; Murphy G S; Robb M L; Innes B L; Birx D L; Hayes C G; Frankel S S. (Viral and Rickettsial Diseases Department, Naval Medical Research Center, Bethesda, Maryland 20889-5607, USA.) Nature medicine, (2000 Jul) Vol. 6, No. 7, pp. 816-20. Journal code: 9502015. ISSN: 1078-8956. Pub. country: United States. Language: English.

AB **Dengue** virus (DV), an arthropod-borne flavivirus, causes a febrile illness for which there is no antiviral treatment and no vaccine. Macrophages are important in **dengue** pathogenesis; however, the initial target cell for DV infection remains unknown. As DV is introduced into human skin by mosquitoes of the genus Aedes, we undertook experiments to determine whether human dendritic cells (DCs) were permissive for the growth of DV. Initial experiments demonstrated that blood-derived DCs were 10-fold more permissive for DV infection than were monocytes or macrophages. We confirmed this with human skin DCs (Langerhans cells and dermal/interstitial DCs). Using cadaveric human skin explants, we exposed skin DCs to DV ex vivo. Of the human leukoctye antigen DR-positive DCs that migrated from the skin, emigrants from both dermis and epidermis, 60-80% expressed DV antigens. These observations were supported by histologic findings from the skin rash of a human subject who received an **attenuated** tetravalent **dengue** vaccine. Immunohistochemistry of the skin showed CD1a-positive DCs double-labeled with an antibody against DV envelope glycoprotein. These data demonstrate that human skin DCs are permissive for DV infection, and provide a potential mechanism for the transmission of DV into human skin.

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=> e kanesa-thasan n/au
E1          18     KANESA THASAN N/AU
E2           7     KANESA THASAN NIRANJAN/AU
E3           0 --> KANESA-THASAN N/AU
E4           3     KANESADA H/AU
E5           6     KANESADA K/AU
E6           1     KANESAKA E/AU
E7           4     KANESAKA I/AU
E8           3     KANESAKA ISAO/AU
E9           3     KANESAKA M/AU
E10          1     KANESAKA MAKI/AU
E11          5     KANESAKA N/AU
E12          3     KANESAKA NAOTO/AU

=> s e1-e2
            18 "KANESA THASAN N"/AU
             7 "KANESA THASAN NIRANJAN"/AU
L48         25 ("KANESA THASAN N"/AU OR "KANESA THASAN NIRANJAN"/AU)

=> s l48 and dengue
          5433 DENGUE
L49         17 L48 AND DENGUE

=> s l49 and attenuat?
        123198 ATTENUAT?
L50          9 L49 AND ATTENUAT?

=> d l50,cbib,ab,1-9
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L50 ANSWER 1 OF 9 MEDLINE on STN
2006603062. PubMed ID: 17012873. Live **attenuated** chimeric yellow fever **dengue** type 2 (ChimeriVax-DEN2) vaccine: Phase I clinical trial for safety and immunogenicity: effect of yellow fever pre-immunity in induction of cross neutralizing antibody responses to all 4 **dengue** serotypes. Guirakhoo Farshad; Kitchener Scott; Morrison Dennis; Forrat Remi; McCarthy Karen; Nichols Richard; Yoksan Sutee; Duan Xiaochu; Ermak Thomas H; **Kanesa-Thasan Niranjan**; Bedford Philip; Lang Jean; Quentin-Millet Marie-Jose; Monath Thomas P. (Acambis, Inc., Cambridge, Massachusetts 02139, USA.. Farshad.Guirakhoo@acambis.com) . Human

vaccines, (2006 Mar-Apr) Vol. 2, No. 2, pp. 60-7. Electronic Publication: 2006-03-15. Journal code: 101265291. ISSN: 1554-8600. Pub. country: United States. Language: English.

AB A randomized double-blind Phase I Trial was conducted to evaluate safety, tolerability, and immunogenicity of a yellow fever (YF)-**dengue** 2 (DEN2) chimera (ChimeriVax-DEN2) in comparison to that of YF vaccine (YF-VAX). Forty-two healthy YF naive adults randomly received a single dose of either ChimeriVax-DEN2 (high dose, 5 log plaque forming units [PFU] or low dose, 3 log PFU) or YF-VAX by the subcutaneous route (SC). To determine the effect of YF preimmunity on the ChimeriVax-DEN2 vaccine, 14 subjects previously vaccinated against YF received a high dose of ChimeriVax-DEN2 as an open-label vaccine. Most adverse events were similar to YF-VAX and of mild to moderate intensity, with no serious side-effects. One hundred percent and 92.3% of YF naive subjects inoculated with 5.0 and 3.0 log10 PFU of ChimeriVax-DEN2, respectively, seroconverted to wt DEN2 (strain 16681); 92% of subjects inoculated with YF-VAX seroconverted to YF 17D virus but none of YF naive subjects inoculated with ChimeriVax-DEN2 seroconverted to YF 17D virus. Low seroconversion rates to heterologous DEN serotypes 1, 3 and 4 were observed in YF naive subjects inoculated with either ChimeriVax-DEN2 or YF-VAX. In contrast, 100% of YF immune subjects inoculated with ChimeriVax-DEN2 seroconverted to all 4 DEN serotypes. Surprisingly, levels of neutralizing antibodies to DEN 1, 2 and 3 viruses in YF immune subjects persisted after 1 year. These data demonstrated that (1) the safety and immunogenicity profile of the ChimeriVax-DEN2 vaccine is consistent with that of YF-VAX, and (2) preimmunity to YF virus does not interfere with ChimeriVax-DEN2 immunization, but induces a long lasting and cross neutralizing antibody response to all 4 DEN serotypes. The latter observation can have practical implications toward development of a **dengue** vaccine.

L50 ANSWER 2 OF 9 MEDLINE on STN

2005354017. PubMed ID: 16005749. An evaluation of **dengue** type-2 inactivated, recombinant subunit, and live-**attenuated** vaccine candidates in the rhesus macaque model. Robert Putnak J; Coller Beth-Ann; Voss Gerald; Vaughn David W; Clements David; Peters Iain; Bignami Gary; Houng Hou-Shu; Chen Robert C-M; Barvir David A; Seriwatana Jitvimol; Cayphas Sylvie; Garcon Nathalie; Gheysen Dirk; **Kanesa-Thasan Niranjan**; McDonell Mike; Humphreys Tom; Eckels Kenneth H; Prieels Jean-Paul; Innis Bruce L. (Walter Reed Army Institute of Research, Division of Communicable Diseases and Immunology, 503 Robert Grant Avenue, Silver Spring, MD 20910, USA.. robert.putnak@na.amedd.army.mil) . Vaccine, (2005 Aug 15) Vol. 23, No. 35, pp. 4442-52. Journal code: 8406899. ISSN: 0264-410X. Pub. country: Netherlands. Language: English.

AB The safety, immunogenicity, and protective efficacy of two non-replicating antigen-based vaccines and one live-**attenuated** virus (LAV) vaccine for **dengue** type-2 (**dengue**-2) virus were evaluated in the rhesus macaque model. The non-replicating vaccines consisted of whole, purified inactivated virus (PIV) and a recombinant subunit protein containing the amino-(N)-terminal 80% of envelope protein (r80E), each formulated with one of five different adjuvants. Each formulation was administered to three animals on a 0, 3-month schedule. Following the primary immunizations, 37 of 39 animals demonstrated **dengue**-2 virus neutralizing antibodies. After the booster immunizations all animals had **dengue** neutralizing antibodies with peak titers ranging from 1:100 to 1:9700. The highest neutralizing antibody titers were observed in the groups that received r80E antigen formulated with AS04, AS05, or AS08 adjuvant, and PIV formulated with AS05 or AS08 adjuvant. These newer adjuvants are based on alum, fraction QS-21 of saponin, and monophosphoryl lipid A (MPL). Protection was evaluated by **dengue**-2 virus challenge 2 months after the booster by the measurement of circulating virus (viremia) and post-challenge immune responses. Several groups exhibited nearly complete protection against viremia by bioassay, although there was evidence for challenge virus replication by Taqmantrade mark and immunological assays. None of the vaccines conferred sterile immunity.

L50 ANSWER 3 OF 9 MEDLINE on STN

2004040706. PubMed ID: 14740955. Phase I trial of 16 formulations of a tetravalent live-**attenuated dengue** vaccine. Edelman Robert; Wasserman Steven S; Bodison Sacared A; Putnak Robert J; Eckels Kenneth H; Tang Douglas; **Kanesa-Thasan Niranjan**; Vaughn David W; Innis Bruce L; Sun Wellington. (Department of Medicine and the Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland 21201, USA.. redelman@medicine.umaryland.edu) . The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 48-60. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United

States. Language: English.

AB Laboratory-**attenuated** strains of each of the four **dengue** serotypes previously tested as monovalent vaccines in volunteers were combined and tested for immunogenicity, safety, and reactogenicity in 16 dosage combinations. Tetravalent vaccines made using combinations of high (10(5-6) plaque-forming units [PFU]/dose) or low (10(3.5-4.5) PFU/dose) dosage formulations of each of the four viruses were inoculated in 64 flavivirus non-immune adult volunteers to determine which, if any, formulation raised neutralizing antibodies in at least 75% of volunteers to at least three of four **dengue** serotypes following one or two inoculations. Such formulations, if safe and sufficiently non-reactogenic, would be considered for an expanded Phase II trial in the future. Formulations 1-15 were each inoculated into three or four volunteers (total = 54) on days 0 and 28. Formulation 16 was tested in 10 volunteers, five volunteers inoculated on days 0 and 30, one volunteer on days 0 and 120, and four volunteers on days 0, 30, and 120. Blood was drawn for serologic assays immediately before and one month after each vaccination, and for viremia assay on day 10 after each vaccination. The 16 formulations were safe, but variably reactogenic after the first vaccination, and nearly non-reactogenic after the second and third vaccinations. Reactogenicity was positively correlated with immunogenicity. Similar proportions of volunteers seroconverted to **dengue**-1 (69%), **dengue**-2 (78%), and **dengue**-3 (69%), but significantly fewer volunteers seroconverted to **dengue**-4 (38%). The geometric mean 50% plaque reduction neutralization test titers in persons who seroconverted were significantly higher to **dengue**-1 (1:94) than to **dengue**-2 (1:15), **dengue**-3 (1:10), and **dengue**-4 (1:2). Seven formulations met the serologic criteria required for an expanded trial, and three of these were sufficiently **attenuated** clinically to justify further testing.

L50 ANSWER 4 OF 9 - MEDLINE-*on* STN

2004040704. PubMed ID: 14740953. Atypical antibody responses in **dengue** vaccine recipients. **Kanesa-Thasan N**; Sun W; Ludwig G V; Rossi C; Putnak J R; Mangiafico J A; Innis B L; Edelman R. (Walter Reed Army Institute of Research, Washington, District of Columbia, USA.. niranjan.kanesa-thasan@det.amedd.army.mil) . The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 32-8. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Eight of 69 (12%) healthy adult volunteers vaccinated with monovalent live-**attenuated** **dengue** virus (DENV) vaccine candidates had atypical antibody responses, with depressed IgM:IgG antibody ratios and induction of high-titer hemagglutination-inhibiting and neutralizing (NT) antibodies to all four DENV serotypes. These features suggested flavivirus exposure prior to DENV vaccination, yet no volunteer had a history of previous flavivirus infection, flavivirus vaccination, or antibody to flaviviruses evident before DENV vaccination. Moreover, production of antibody to DENV by atypical responders (AR) was not accelerated compared with antibody responses in the 61 flavivirus-naive responders (NR). Further evaluation revealed no differences in sex, age, race, DENV vaccine candidate received, or clinical signs and symptoms following vaccination between AR and NR. However, viremia was delayed at the onset in AR compared with NR. A comparative panel of all AR and five randomly selected NR found flavivirus cross-reactive antibody after vaccination only in AR. Unexpectedly, six of eight AR had NT antibodies to yellow fever virus (YFV) > 1:10 before vaccination while NR had none (P = 0.04). The AR also universally demonstrated YFV NT antibody titers > or = 1:160 after DENV vaccination, whereas four of five NR failed to seroconvert (P = 0.02). Yellow fever virus priming broadens the antibody response to monovalent DENV vaccination. The effect of flavivirus priming on the clinical and immunologic response to tetravalent DENV vaccine remains to be determined.

L50 ANSWER 5 OF 9 MEDLINE on STN

2004040703. PubMed ID: 14740952. Vaccination of human volunteers with monovalent and tetravalent live-**attenuated** **dengue** vaccine candidates. Sun Wellington; Edelman Robert; **Kanesa-Thasan Niranjan**; Eckels Kenneth H; Putnak J Robert; King Alan D; Houng Huo-Shu; Tang Douglas; Scherer John M; Hoke Charles H Jr; Innis Bruce L. (Department of Virus Diseases, Walter Reed Army Institute of Research, Silver Spring, Maryland 20910, USA.. wellington.sun@na.amedd.army.mil) . The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 24-31. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Four serotypes of monovalent live **attenuated** **dengue** virus vaccine candidates were tested for reactogenicity and immunogenicity in 49

flavivirus. non-immune adult human volunteers. The four monovalent candidates were then combined into a tetravalent formulation and given to another 10 volunteers. Neutralizing antibody seroconversion rates after a single-dose monovalent vaccination ranged from 53% to 100%. Solicited reactogenicity was scored by each volunteer. A composite index, the Reactogenicity Index, was derived by these self-reported scores. Reactogenicity differed among the four serotype candidates with serotype-1 associated with the most vaccine related side effects. A second dose of monovalent vaccines at either 30 days or 90 days was much less reactogenic but did not significantly increase seroconversion rates. Seroconversion rates in the 10 volunteers who received a single dose of tetravalent vaccine ranged from 30% to 70% among the four serotypes. Similar to the monovalent vaccines, a second dose of the tetravalent vaccine at one month was less reactogenic and did not increase seroconversion. A third dose of the tetravalent vaccine at four months resulted in three of four volunteers with trivalent or tetravalent high-titer neutralizing antibody responses.

L50 ANSWER 6 OF 9 MEDLINE on STN

2004040702. PubMed ID: 14740951. Phase 1 studies of Walter Reed Army Institute of Research candidate **attenuated dengue** vaccines: selection of safe and immunogenic monovalent vaccines. **Kanesa-Thasan N**; Edelman R; Tacket C O; Wasserman S S; Vaughn D W; Coster T S; Kim-Ahn G J; Dubois D R; Putnak J R; King A; Summers P L; Innis B L; Eckels K H; Hoke C H Jr. (Walter Reed Army Institute of Research, Washington, District of Columbia, USA.. niranjan.kanesa-thasan@det.amedd.army.mil) . The American journal of tropical medicine and hygiene, (2003 Dec) Vol. 69, No. 6 Suppl, pp. 17-23. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB We describe the results of initial safety testing of 10 live-**attenuated dengue** virus (DENV) vaccine candidates modified by serial passage in primary dog kidney (PDK) cells at the Walter Reed Army Institute of Research. The Phase 1 studies, conducted in 65 volunteers, were designed to select an **attenuated** vaccine candidate for each DENV serotype. No recipient of the DENV candidate vaccines sustained serious injury or required treatment. Three vaccine candidates were associated with transient idiosyncratic reactions in one volunteer each, resulting in their withdrawal from further clinical development. Increasing PDK cell passage of DENV-1, DENV-2, and DENV-3 candidate vaccines increased **attenuation** for volunteers, yet also decreased infectivity and immunogenicity. This effect was less clear for DENV-4 candidate vaccines following 15 and 20 PDK cell passages. Only one passage level each of the tested DENV-2, -3, and -4 vaccine candidates was judged acceptably reactogenic and suitable for expanded clinical study. Subsequent studies with more recipients will further establish safety and immunogenicity of the four selected vaccine candidates: DENV-1 45AZ5 PDK 20, DENV-2 S16803 PDK 50, DENV-3 CH53489 PDK 20, and DENV-4 341750 PDK 20.

L50 ANSWER 7 OF 9 MEDLINE on STN

2002386869. PubMed ID: 12135278. Short report: absence of protective neutralizng antibodies to West Nile virus in subjects following vaccination with Japanese encephalitis or **dengue** vaccines. **Kanesa-Thasan N**; Putnak J R; Mangiafico J A; Saluzzo J E; Ludwig G V. (Walter Reed Army Institute of Research, Washington, District of Columbia 20307-5100, USA,.. niranjan.kanesa-thasan@det.amedd.army.mil) . The American journal of tropical medicine and hygiene, (2002 Feb) Vol. 66, No. 2, pp. 115-6. Journal code: 0370507. ISSN: 0002-9637. Pub. country: United States. Language: English.

AB Protection of individuals against West Nile (WN) encephalitis is an emerging concern in the United States and Europe. We investigated whether immunization with licensed inactivated Japanese encephalitis (JE) vaccine or experimental live **attenuated dengue** vaccines resulted in induction of cross-neutralizing antibodies against WN virus. Protective neutralizing antibody titers to WN virus were not detected in any volunteer despite successful immunization to related flaviviruses. Vaccination against JE or **dengue** is unlikely to prevent WN virus infection but may still protect against disease.

L50 ANSWER 8 OF 9 MEDLINE on STN

2001493783. PubMed ID: 11535318. Induction of T lymphocyte responses to **dengue** virus by a candidate tetravalent live **attenuated dengue** virus vaccine. Rothman A L; **Kanesa-thasan N**; West K; Janus J; Saluzzo J F; Ennis F A. (Center for Infectious Disease and Vaccine Research, Rm. S5-326, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA.. alan.rothman@umassmed.edu) . Vaccine, (2001 Sep

14) Vol. 19, No. 32, pp. 4694-9. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB Development of a safe and immunogenic tetravalent **dengue** virus (DV) vaccine has been designated as a priority by the World Health Organization. We characterized the T cell response to DV induced by a candidate live **attenuated** tetravalent DV vaccine as part of a phase I study. Proliferation and cytotoxic T lymphocyte (CTL) responses to multiple DV serotypes were detected in six of six and four of four subjects studied, respectively. Proliferation responses were higher to DV serotypes 1 and 3 than to serotypes 2 and 4. CTL responses were higher to DV serotypes 2 and 3 than to serotype 1, and included serotype cross-reactive responses. Production of interferon-gamma, but not IL-4, was observed in response to DV stimulation. This candidate vaccine is immunogenic for both CD4+ and CD8+ T lymphocytes. However, T cell responses to the four DV serotypes were not equivalent, suggesting that the vaccine could be further optimized.

L50 ANSWER 9 OF 9 MEDLINE on STN

2001222564. PubMed ID: 11312014. Safety and immunogenicity of **attenuated dengue** virus vaccines (Aventis Pasteur) in human volunteers. **Kanesa-thasan N**; Sun W; Kim-Ahn G; Van Albert S; Putnak J R; King A; Raengsakulsrach B; Christ-Schmidt H; Gilson K; Zahradnik J M; Vaughn D W; Innis B L; Saluzzo J F; Hoke C H Jr. (Walter Reed Army Institute of Research, Washington, DC, USA.. niranjan.kanesa-thasan@na.amedd.army.mil) . Vaccine, (2001 Apr 30) Vol. 19, No. 23-24, pp. 3179-88. Journal code: 8406899. ISSN: 0264-410X. Pub. country: England: United Kingdom. Language: English.

AB A randomized, controlled, double-blinded study was conducted to determine safety and immunogenicity of five live **attenuated dengue** vaccines produced by Aventis Pasteur (AvP). The study was completed with 40 flavivirus non-immune volunteers: five recipients of each monovalent (**dengue**-1, **dengue**-2, **dengue**-3, or **dengue**-4) vaccine, ten recipients of tetravalent (**dengue**-1, **dengue**-2, **dengue**-3, and **dengue**-4) vaccine, and ten recipients of vaccine vehicle alone. All vaccines were administered in a single subcutaneous dose (range, 3.6-4.4 log(10) plaque forming units). No serious adverse reactions occurred in volunteers followed for 6 months after vaccination. Five vaccine recipients developed fever (T > or = 38.0 degrees C), including four tetravalent vaccinees between days 8 and 10 after vaccination. **Dengue**-1, **dengue**-2, **dengue**-3, or **dengue**-4 vaccine recipients reported similar frequency of mild symptoms of headache, malaise, and eye pain. Tetravalent vaccinees noted more moderate symptoms with onset from study days 8-11 and developed maculopapular rashes distributed over trunk and extremities. Transient neutropenia (white blood cells < 4000/mm3) was noted after vaccination but not thrombocytopenia (platelets < 100,000/mm3). All **dengue**-3, **dengue**-4, and tetravalent vaccine recipients were viremic between days 7 and 12 but viremia was rarely detected in **dengue**-1 or **dengue**-2 vaccinees. All **dengue**-2, **dengue**-3, and **dengue**-4, and 60% of **dengue**-1 vaccine recipients developed neutralizing and/or immunoglobulin M antibodies. All tetravalent vaccine recipients were viremic with **dengue**-3 virus and developed neutralizing antibodies to **dengue**-3 virus. Seven volunteers also had multivalent antibody responses, yet the highest antibody titers were against **dengue**-3 virus. The AvP live **attenuated dengue** virus vaccines are safe and tolerable in humans. The live **attenuated** tetravalent **dengue** vaccine was most reactogenic, and preferential replication of **dengue**-3 virus may have affected its infectivity and immunogenicity.

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(FILE 'HOME' ENTERED AT 12:50:19 ON 29 DEC 2006)

FILE 'USPATFULL' ENTERED AT 12:50:29 ON 29 DEC 2006

L1	3111	S DENGUE
L2	6	S L1 AND 45AZ5
L3	6	S L2 AND PDK-27
L4	14	S L1 AND S16803
L5	9	S L4 NOT L2
L6	1	S L5 AND PDK-50
L7	12	S L1 AND CH53489
L8	7	S L7 NOT (L3 OR L6)
L9	0	S L8 AND PDK-20
L10	9	S L1 AND 341750

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L11           4 S L10 NOT (L3 OR L6)
L12          95 S L1 AND TETRAVALENT
L13           2 S L12 AND TETRAVALENT/CLM
L14           1 S L13 NOT (L3 OR L5 OR L8)

     FILE 'WPIDS' ENTERED AT 12:57:32 ON 29 DEC 2006
L15         551 S DENGUE
L16           2 S L15 AND 45AZ5
L17           2 S L15 AND S16803
L18           0 S L17 NOT L16
L19           1 S L15 AND CH53489
L20           1 S L19 NOT L16
L21           4 S L15 AND 341750
L22           2 S L21 NOT (L16 OR L17 OR L19)
L23           6 S L15 AND TETRAVALENT
L24           6 S L23 NOT (L16 OR L17 OR L19)

     FILE 'MEDLINE' ENTERED AT 13:05:50 ON 29 DEC 2006
L25        5433 S DENGUE
L26         197 S L25 AND ATTENUATE?
L27          19 S L26 AND (SERIAL PASSAGE?)
L28           5 S L27 AND (PRIMARY KIDNEY CELLS)
L29          12 S L27 AND (PRIMARY DOG KIDNEY)
L30           7 S L29 NOT L28
                E ECKELS K/AU
L31           8 S E5
L32           7 S L31 AND DENGUE
                E PUTNAK J R/AU
L33          21 S E3-E4
L34          11 S L33 AND DENGUE
L35           9 S L34 NOT L31
                E DUBOIS D R/AU
                E DUBOIS DORIA R/AU
L36           1 S E3
                E INNIS B L/AU
L37          22 S E5-E6
L38          10 S L37 AND DENGUE
L39           7 S L38 AND ATTENUATE?
L40           1 S L39 NOT (L31 OR L33 OR L36)
                E HOKE C H/AU
L41          81 S E2-E5
L42          25 S L41 AND DENGUE
L43          12 S L42 AND ATTENUATE?
L44          10 S L43 NOT (L31 OR L33 OR L36 OR L37)
                E SUN W/AU
L45         313 S E3
L46           7 S L45 AND DENGUE
L47           4 S L46 AND ATTENUAT?
                E KANESA-THASAN N/AU
L48          25 S E1-E2
L49          17 S L48 AND DENGUE
L50           9 S L49 AND ATTENUAT?

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ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y
STN INTERNATIONAL LOGOFF AT 13:22:41 ON 29 DEC 2006
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